Title: A Phase 1b, Open-Label, Dose Escalation, Multi-arm Study of MLN4924 Plus Docetaxel, Gemcitabine, or Combination of Carboplatin and Paclitaxel in Patients With Solid Tumors

NCT Number: NCT01862328

Protocol Approve Date: 17 October 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

CLINICAL STUDY PROTOCOL C15010 AMENDMENT 1

MLN4924

A Phase 1b, Open-Label, Dose Escalation, Multi-arm Study of MLN4924 Plus Docetaxel, Gemcitabine, or Combination of Carboplatin and Paclitaxel in Patients With Solid Tumors

Protocol Number:	C15010
Indication:	Solid tumors
Phase:	1b
Sponsor:	Millennium Pharmaceuticals, Inc.
Therapeutic Area:	Oncology

Protocol History

Original	08 March 2013
Amendment 1	17 October 2017

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Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

PPD

Rationale for Amendment 1

The original protocol was written in 2013 and was designed with procedures and assessments requiring many visits. As of 09 June 2017, 2 patients with solid tumors remain on study after completing at least 12 cycles of MLN4924 single-agent treatment in Arm 2. The sponsor and investigators have therefore determined, on the basis of the accumulated experience to date, that it is appropriate at this time to reduce the frequency of procedures and clinic visits with the intention of lessening patient burden, increasing patient retention, and more closely aligning with clinical practice. The primary reason for Amendment 1 is to add flexibility to relieve treatment fatigue for the 2 patients remaining in this study beyond the initially planned 12 cycles of treatment, and a new Schedule of Events table has been generated to reflect these changes. Clarifications regarding the duration of gemcitabine administration and the timing of urine safety assessments previously specified in administrative letters to the United States Food and Drug Administration have also been included to reflect study conduct.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes, the rationale for each change, and where the changes are located, see Section 15.10.

Changes in Amendment 1

After completion of Cycle 12, the following changes will be applicable:

1. Extend the 2-day window for scheduling issues (eg, inclement weather, holidays, vacations, or other administrative reasons) to 2 weeks; treatment breaks of up to 4 weeks may be permitted after discussion between the investigator and the project clinician or designee, and the investigator will confirm patient eligibility for continued treatment upon return, before treatment.
2. Reduce the frequency of disease response assessments from every 3 cycles to every 6 cycles.
3. Reduce the frequency of hematology and clinical chemistry assessments and physical examinations.
4. Remove ketones, bilirubin, urobilinogen, and glucose from the Urinalysis With Microscopic Analysis parameters.
5. Add a ±10-minute window to the MLN4924 infusion duration.
6. Remove the requirement for independent data monitoring committee monitoring.
7. Adjust contraception requirements to be consistent with Clinical Trial Facilitation Group recommendations.
8. Update the description of the drug product.
9. Update the investigator responsibilities for compliance with updated International Council for Harmonisation guidelines.
10. Update the description of the dose-limiting toxicity observed in Study C15003 to be consistent with final data.

11. Update vital signs assessments to allow measurements to be taken with the patient in the supine or sitting position.
12. Clarify that if needed, a red blood cell transfusion must occur at least 1 day before study drug administration.
13. Updated clinical laboratory evaluations.
14. Remove statins, known breast cancer resistance protein substrates, moderate and strong inhibitors of cytochrome P450 3A4, and inhibitors of P-glycoprotein from the list of excluded concomitant medications.
15. Replace references to the Safety Management Attachment with references to the Development Core Safety Information.
16. Update the description of the Safety Management Team to be consistent with current preferred language and to reflect its cross-functional nature.
17. Update contact information for product complaints.
18. Update contact information for serious adverse event reporting.
19. Update the risks of MLN4924 therapy to be consistent with the current version of the Investigator's Brochure (IB).
20. Clarify the duration of gemcitabine administration per the prescribing information guidelines, as stated in Administrative Letter 1.
21. Clarify the collection time points for the urine safety assessment at screening and Cycle 1 Day 1 (predose), as stated in Administrative Letter 2.

PROTOCOL SUMMARY

Study Title: A Phase 1b, Open-Label, Dose Escalation, Multi-arm Study of MLN4924 Plus Docetaxel, Gemcitabine, or Combination of Carboplatin and Paclitaxel in Patients With Solid Tumors

Number of Patients: Approximately 69 patients

Study Objectives

Primary Objectives

- To establish the maximum tolerated dose (MTD) and assess the safety and tolerability of MLN4924 in combination with docetaxel in patients with solid tumors
- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with paclitaxel and carboplatin in patients with solid tumors
- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with gemcitabine in patients with solid tumors

Secondary Objectives

- To evaluate disease response that may be observed with the combination of MLN4924 and docetaxel
- To evaluate disease response that may be observed with the combination of MLN4924, paclitaxel, and carboplatin
- To evaluate disease response that may be observed with the combination of MLN4924 and gemcitabine
- To measure plasma MLN4924 concentrations to contribute to a population pharmacokinetic (PK) analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine in patients with solid tumors

Exploratory Objectives

CCI [redacted]

Overview of Study Design: This is an open-label, multicenter, phase 1b, dose escalation study of MLN4924 in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine in adult patients with solid tumors (patients in the carboplatin lead-in cohort will receive MLN4924 + carboplatin only). The patient population will consist of patients 18 years of age or older with nonhematologic malignancies who, according to the investigator's medical judgment, could potentially benefit from treatment with any of the 3 standard of care (SoC) therapies being studied.

It is expected that approximately 69 patients will be enrolled in this study. During the dose escalation portion of this study, the following dose levels of intravenous (IV) MLN4924 are planned to be studied in combination with docetaxel (Arm 1), paclitaxel + carboplatin (Arm 2), or gemcitabine

(Arm 3).

MLN4924 + Docetaxel (Arm 1): A total of 4 dose levels of IV MLN4924 (15, 25, 37, and 50 mg/m^2) are planned to be studied in combination with 75 mg/m^2 of docetaxel. On Day 1 of each cycle when both drugs are administered, docetaxel will be administered first at a dose of 75 mg/m^2 IV over 1 hour. After a mandatory approximately 15-minute time out (MLN4924-free period), MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days. No dose reduction of MLN4924 below 15 mg/m^2 is allowed.

MLN4924 + Carboplatin Lead-in Cohort (before Arm 2): Before patients are enrolled in Arm 2 with paclitaxel + carboplatin, a cohort of approximately 3 to 6 patients will be treated with AUC6 dose of carboplatin in combination with MLN4924 at a dose of 15 mg/m^2. On Day 1 of each cycle, both compounds will be given. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days. If 1 dose-limiting toxicity (DLT) is seen in this cohort, 3 additional patients will be treated with the same combination regimen. The carboplatin dose may be reduced to AUC5 for safety as needed. No dose reduction of MLN4924 below 15 mg/m^2 is allowed. No dose escalation of MLN4924 is planned in this cohort. The only chemotherapy agent that patients in this lead-in cohort will receive is carboplatin; these patients will not enroll in the MLN4924 + paclitaxel + carboplatin phase (Arm 2).

Observing no more than 1 DLT in this lead-in cohort will trigger enrollment in Arm 2 at AUC6 (MLN4924 [15 mg/m^2] + paclitaxel [200 mg/m^2] + carboplatin [AUC6]), and patients will be treated as described below for Arm 2.

If a total of 2 or more DLTs are observed in this cohort, enrollment in Arm 2 will open at reduced paclitaxel and carboplatin doses (MLN4924 [15 mg/m^2] + paclitaxel [175 mg/m^2] + carboplatin [AUC5]), and patients will be treated as described below in Arm 2.

MLN4924 + Paclitaxel + Carboplatin (Arm 2): During the dose escalation phase, a total of 4 dose levels of IV MLN4924 (15, 25, 37, and 50 mg/m^2) are planned to be studied in combination with paclitaxel and carboplatin. On Day 1 of each cycle when all 3 drugs are administered, paclitaxel is given first at a dose of 200 mg/m^2 (or 175 mg/m^2, if the dose was reduced in the carboplatin lead-in cohort) IV over 3 hours followed by carboplatin AUC6 (or AUC5 if the dose was reduced in carboplatin lead-in cohort) over 30 minutes. After a mandatory approximately 15-minute time out (MLN4924-free period) after carboplatin administration, MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days.

MLN4924 + Gemcitabine (Arm 3): A total of 4 dose levels of IV MLN4924 (25, 50, 75, and 100 mg/m^2) are planned to be studied in combination with 1000 mg/m^2 of gemcitabine. Gemcitabine will be administered IV at a dose of 1000 mg/m^2 over 30 to 60 minutes or per current prescribing guidelines. After a 15-minute time out, MLN4924 will be administered. Patients will receive both agents on Days 1, 8, and 15, and the duration of each cycle will be 28 days.

After the determination of the MTD of MLN4924 with docetaxel (Arm 1), paclitaxel + carboplatin (Arm 2), and gemcitabine (Arm 3), approximately 6 additional patients will be enrolled to each arm, for a total of approximately 12 patients treated in each arm at the MTD to more fully characterize the safety, tolerability, and PK of MLN4924 in combination with each SoC regimen and to evaluate disease response.

An adaptive approach using a continual reassessment method (CRM) will be used for dose escalation (see Section 6.4). The dose toxicity relationship and the predicted maximum tolerated dose (PMTD) level will be updated as new data become available. The recommendation to escalate, de-escalate, or expand at the same dose level will be determined by comparing the PMTD level from the dose toxicity model to the prespecified dose levels. From the starting dose, subsequent increases will be made according to the dose levels indicated for each arm; however, for safety reasons, no dose level

will be skipped, and a minimum of 3 patients is required before escalating to the next dose level. Once at least 6 patients are treated at any dose level and the algorithm does not recommend escalation or de-escalation, this dose level may be considered the MTD.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.[1]

Throughout the study, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and adverse events (AEs) will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained and assessed to evaluate the safety and tolerability of MLN4924 in combination with docetaxel, paclitaxel + carboplatin, and gemcitabine (patients in the carboplatin lead-in cohort will receive MLN4924 + carboplatin only).

Blood samples (sparse sampling) for the determination of MLN4924 plasma concentrations and, if appropriate, its metabolites will be collected from each patient during Cycle 1 of treatment to contribute to a population PK analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine. During the dose escalation portion of the study (excluding the Arm 2 carboplatin lead-in cohort), blood samples will be collected from each patient for the determination of MLN4924 plasma concentrations during the first cycle of treatment at the time points indicated in the Schedules of Events. During the MTD expansion portion of the study, serial blood samples will be collected from all patients at the time points indicated in the Schedules of Events before and after the start of MLN4924 infusion.

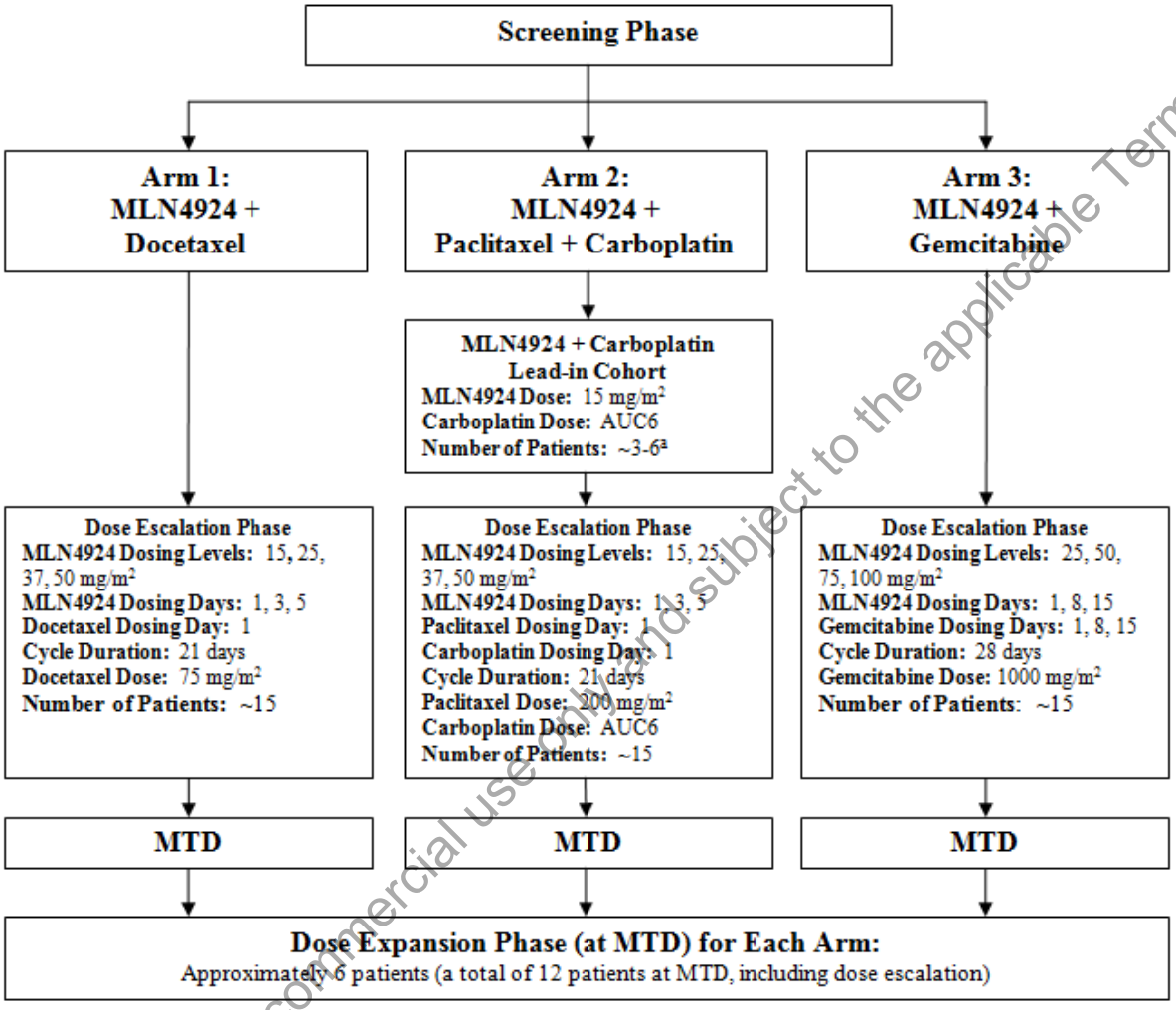
Computed tomography (CT) scans with IV contrast of the chest, abdomen, and pelvis will be performed during screening. CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter (Cycles 4-12) or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 1), and at the End of Study (EOS) visit. Additional CT scans may be performed, per the investigator's discretion, if clinically indicated. Magnetic resonance imaging (MRI) may be used to evaluate sites of disease. Tumor response will be assessed by the investigator at these times using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

Paraffin-embedded tumor tissue or unstained slides of the tumor tissue will be collected at screening to enable genetic characterization of the patient's tumor and to evaluate expression levels of candidate response biomarkers [redacted]

Study Population: Patients 18 years of age or older who have a histologically or cytologically confirmed metastatic or locally advanced and incurable solid tumor that is felt to be appropriate for treatment with 1 of the 3 chemotherapy regimens in this study, or have progressed despite standard therapy, or for whom conventional therapy is not considered effective.

Duration of Study: The maximum duration of treatment will be 12 cycles; however, if it is determined after discussion between the investigator and the sponsor that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy or receive MLN4924 as a single agent beyond 12 cycles.

STUDY OVERVIEW DIAGRAM



Abbreviations: AUC = area under the curve; DLT = dose limiting toxicity; MTD = maximum tolerated dose

a. If no DLT is observed in the first 3 patients during the lead-in phase, dose escalation of MLN4924 in combination with paclitaxel and carboplatin will open for enrollment. If 1 DLT is observed, 3 additional patients will be enrolled in the lead-in phase.

SCHEDULES OF EVENTS

Cycle 1: Arm 1 and Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

		Treatment Cycle (21 Days)							
		Week 1					Week 2	Week 3	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	End of Study[b]
Study Drug Administration									
MLN4924 Infusion[c]		X			X	X			
Docetaxel Administration (Arm 1)[c]		X							
Carboplatin Administration (Arm 2 Lead-In)[c]		X							
Paclitaxel + Carboplatin Administration (Arm 2)[c]		X							
Procedures									
Informed Consent	X								
Inclusion/Exclusion	X								
Demographics	X								
Complete Medical History	X								
Full Physical Examination	X								X
Symptom-directed Physical Examination		X		X	X	X	X		

Cycle 1: Arm 1 and Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Screening[a]	Treatment Cycle (21 Days)							End of Study[b]
		Week 1					Week 2	Week 3	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	
Pregnancy Test (Females of Child-bearing Potential Only)	X								
Height	X								
Weight[d]	X	X[e]							X
ECOG Performance Status	X	X[e]							X
Vital Signs[f]	X	X[e]	X	X	X	X			X
12-Lead ECG[g]	X	X[e]	X		X	X			
Concomitant Medications/Therapy		Recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)							
Hematology[h]	X	X[e]		X	X	X	X	X	X
Coagulation[i]	X	X[e]							
Clinical Chemistry Panel[j]	X	X[e]	X	X	X	X	X	X	X
Urinalysis With Microscopic Analysis[k]	X	X[e]			X	X			
Urine Safety Assessment[l]	X	X		X	X	X			
Echocardiogram	X								
Serious Pretreatment Events and SAE Collection[m]	Serious pretreatment events and SAEs will be reported from the time informed consent is signed through 30 days (+ 10 days) after the last dose of study drug(s)								
AE Collection[m]		Recorded from the first dose of any study drug through 30 days (+ 10 days) after the last dose of study							

Cycle 1: Arm 1 and Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Screening[a]	Treatment Cycle (21 Days)							End of Study[b]
		Week 1					Week 2	Week 3	
		Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	
		drug(s)							
Blood Samples for PK[n]		X	X	X	X	X			
Biomarker Blood Samples[o]	X								
Banked Tumor Tissue[p]	X								
Tumor Assessment by RECIST (CT/MRI)[q]	X								

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOS=End of Study (visit); hr=hour(s); INR=international normalized ratio; IV=intravenous(ly); min=minute(s); MRI=magnetic resonance imaging; MTD=maximum tolerated dose; PE=physical examination; PK=pharmacokinetic; PT=prothrombin time; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

a Screening assessments will be performed within 28 days before the Day 1 dose of study drugs.

b The EOS visit will occur 30 days (+ 10 days) after the last dose of study drugs or before the start of subsequent therapy for their indication, if that occurs sooner.

c On Day 1, when MLN4924 and chemotherapy agents are administered, chemotherapy will be administered first followed by MLN4924. The infusion of MLN4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced due to toxicities in accordance with Section 6.5. The chemotherapeutic agent may be dose-reduced due to toxicities in accordance with Section 6.5. See Section 6.1 for details of study drug administration. **NOTE: a time-out of approximately 15 minutes is required between end of infusion of chemotherapy regimen and start of infusion of MLN4924.**

d Weight should be measured predose.

e Procedures conducted during screening that are performed within 3 days of Day 1 can also be used as the Day 1 predose evaluation and do not need to be repeated.

f Vital signs are taken immediately before each infusion of docetaxel, paclitaxel, carboplatin, and MLN4924. In addition, vital signs are taken 30 min

Cycle 1: Arm 1 and Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

		Treatment Cycle (21 Days)							
		Week 1					Week 2	Week 3	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	End of Study[b]

(± 10 min) after start of MLN4924 dosing, and 1 hr (± 10 min) after completion of MLN4924 dosing. On Cycle 1 Day 1, additional vital signs should be obtained 3 hours (± 30 min) after completion of MLN4924 dosing. All of these vital signs are taken with the patient in the sitting position. In addition, at predose and 1 hour postdose of MLN4924 administration on Cycle 1 Day 1, orthostatic blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting for approximately 3 to 4 minutes.

g A 12-lead ECG will be performed during screening and on Day 1 before administration (within 3 hours) of chemotherapy regimen, immediately after the infusion of MLN4924 is complete (± 10 min). On Days 3 and 5, 12-lead ECGs will be performed before MLN4924 dosing and 90 min (± 10 min) after the start of MLN4924 infusion.

h Hematology samples will be collected during screening; before dosing with study drug(s) on Days 1, 3, and 5; Day 2; Day 8; Day 15; and at the EOS visit. On Days 1 and 5, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

i A coagulation panel at screening will include the following: PT (INR), aPTT, fibrinogen, and D-dimer. If the initial coagulation screen is positive, subsequent coagulation studies should include all of these parameters. If the initial coagulation screen is negative, subsequent coagulation studies should include only PT (INR) and aPTT.

j Clinical chemistry samples will be collected during screening and before dosing with study drugs on Days 1, 3, and 5. On Days 1 and 5, samples can be drawn within 24 hours predose. In addition, samples will be taken on Day 1 at 3 hours (± 30 min) postinfusion with MLN4924; on Day 2, Day 8, and Day 15; and at the EOS visit. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

k Urinalysis samples will be analyzed at the site's local laboratory.

l Urine samples for safety assessments will be collected at screening; before any study drug dosing on Days 1, 3, and 5; and on Day 2. These samples will be analyzed at a central laboratory.

m Serious pretreatment events (occurring before the first dose of any study drug) will only be reported to CCI [redacted] and will not be entered on the eCRF. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

n See the PK Schedules of Events for all PK collection times: refer to Cycle 1: Arm 1 Dose Escalation Pharmacokinetics Schedule and Cycle 1: Arm 2

Cycle 1: Arm 1 and Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

		Treatment Cycle (21 Days)							
		Week 1					Week 2	Week 3	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	End of Study[b]

Dose Escalation Pharmacokinetics Schedule during the dose escalation phase of the study, and refer to Cycle 1: Arm 1 Maximum Tolerated Dose Expansion Pharmacokinetics Schedule and Cycle 1: Arm 2 MTD Expansion Pharmacokinetics Schedule during the MTD expansion phase of the study. Note that the Day 5 PK collection applies only to the MTD Expansion Phase.

o Two blood samples will be collected: one to generate a plasma sample and the other to generate genomic DNA for assessment of biomarkers of response.

p A specimen of fixed tumor sample will be collected for genetic characterization of the patient's tumor and for assessment of candidate biomarkers of response to MLN4924-containing therapy. Suitable specimens are either a tumor block or 10 to 20 unstained slides.

q CT scans with IV contrast of the chest, abdomen, and pelvis will be performed during screening. If the sites of disease are not adequately imaged by CT, MRI may also be used to evaluate sites of disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1 Day 1, then the results of those scans may be used for the screening assessment.

Cycle 1: Arm 1 Dose Escalation Pharmacokinetics Schedule

Arm 1 (MLN4924 + Docetaxel) Dose Escalation Phase: Cycle 1 Timing of Pharmacokinetic Measurements

	Cycle 1				
			After End of MLN4924 Infusion		
	Pre-infusion	End of MLN4924 Infusion	1.5 hour ± 15 min	3 hour ± 30 min	20 hour ± 2 hour
Day 1	X[a]	X[b]	X	X	
Day 2					X[c]
Day 3	X[d]				

a The sample is to be collected within 1 hour before the start of MLN4924 infusion.

b The sample is to be collected at the end of MLN4924 infusion (immediately before switching off the infusion pump).

c Note that the 20-hour time point after completion of the infusion on Day 1 will actually fall on Day 2.

d The sample is to be collected within 10 minutes before the start of MLN4924 infusion.

Cycle 1: Arm 2 Dose Escalation Pharmacokinetics Schedule

Arm 2 (MLN4924 + Paclitaxel + Carboplatin) Dose Escalation Phase: Cycle 1 Timing of Pharmacokinetic Measurements

	Cycle 1				
			After End of MLN4924 Infusion		
	Pre-infusion	End of MLN4924 Infusion	1.5 hour ± 15 min	3 hour ± 30 min	20 hour ± 2 hour
Day 1	X[a]	X[b]	X	X	
Day 2					X[c]
Day 3	X[d]				

a The sample is to be collected within 1 hour before the start of MLN4924 infusion.

b The sample is to be collected at the end of MLN4924 infusion (immediately before switching off the infusion pump).

c Note that the 20-hour time point after completion of the infusion on Day 1 will actually fall on Day 2.

d The sample is to be collected within 10 minutes before the start of MLN4924 infusion.

Cycle 1: Arm 1 Maximum Tolerated Dose Expansion Pharmacokinetics Schedule
Arm 1 (MLN4924 + Docetaxel) Maximum Tolerated Dose Expansion Phase: Cycle 1 Timing of Pharmacokinetic Measurements

	Cycle 1					
			After End of MLN4924 Infusion			
	Pre-infusion	End of MLN4924 Infusion	1.5 hour ± 15 min	3 hour ± 30 min	7 hour ± 45 min	20 hour ± 2 hour
Day 1	X[a]	X[b]	X	X	X	
Day 2						X[c]
Day 3	X[d]					
Day 5	X[d]	X[b]	X	X	X	
Day 6						X[e]

a The sample is to be collected within 1 hour before the start of MLN4924 infusion.
b The sample is to be collected at the end of MLN4924 infusion (immediately before switching off the infusion pump).
c Note that the 20-hour time point after completion of the infusion on Day 1 will actually fall on Day 2.
d The sample is to be collected within 10 minutes before the start of MLN4924 infusion.
e Note that the 20-hour time point after completion of the infusion on Day 5 will actually fall on Day 6.

Cycle 1: Arm 2 MTD Expansion Pharmacokinetics Schedule

Arm 2 (MLN4924 + Paclitaxel + Carboplatin) Maximum Tolerated Dose Expansion Phase: Cycle 1 Timing of Pharmacokinetic Measurements

	Cycle 1					
			After End of MLN4924 Infusion			
	Pre-infusion	End of MLN4924 Infusion	1.5 hour ± 15 min	3 hour ± 30 min	6 hour ± 45 min	20 hour ± 2 hour
Day 1	X[a]	X[b]	X	X	X	
Day 2						X[c]
Day 3	X[d]					
Day 5	X[d]	X[b]	X	X	X	
Day 6						X[e]

a The sample is to be collected within 1 hour before the start of MLN4924 infusion.
b The sample is to be collected at the end of MLN4924 infusion (immediately before switching off the infusion pump).
c Note that the 20-hour time point after completion of the infusion on Day 1 will actually fall on Day 2.
d The sample is to be collected within 10 minutes before the start of MLN4924 infusion.
e Note that the 20-hour time point after completion of the infusion on Day 5 will actually fall on Day 6.

Cycle 2 and Beyond: Arm 1, and Cycle 2 through Cycle 12: Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Treatment Cycle (21 Days)[a]						
	Week 1				Week 2	Week 3	
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	End of Study[b]
Study Drug Administration							
MLN4924 Infusion (Arm 1 and Arm 2)[c]	X		X	X			
Docetaxel Administration (Arm 1)[c]	X						
Carboplatin Administration (Arm 2 Lead-in)[c]	X						
Paclitaxel + Carboplatin Administration (Arm 2)[c]	X						
Procedures							
Full Physical Examination	X						X
Symptom-directed Physical Examination			X	X			
Weight	X						X
ECOG Performance Status	X						X
Vital Signs[d]	X	X	X	X			X
12-Lead ECG[e]	X	X					
Concomitant Med/Therapy	Recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)						
Hematology[f]	X		X	X	X	X	X
Coagulation[g]	X						
Clinical Chemistry Panel[h]	X		X	X	X	X	X

Cycle 2 and Beyond: Arm 1, and Cycle 2 through Cycle 12: Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Treatment Cycle (21 Days)[a]						
	Week 1				Week 2	Week 3	
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	End of Study[b]
Urinalysis with Microscopic Analysis[i]	X		X	X			
Urine Safety Assessments[j]	X						
SAE Collection[k]	SAEs will be reported from the time informed consent is signed through 30 days (+ 10 days) after the last dose of study drug(s)						
AE Collection[k]	Recorded from the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)						
Tumor Assessment by RECIST (CT/MRI)[l]						X	X

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOS=End of Study (visit); INR=international normalized ratio; IV=intravenous(ly); Med=medication; MRI=magnetic resonance imaging; PE=physical examination; PT=prothrombin time; RESIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

a For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to ≤ Grade 1, to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician (Section 6.5).

b The EOS visit will occur 30 days (+ 10 days) after the last dose of study drug(s) or before the start of subsequent therapy for their indication, if that occurs sooner.

c On Day 1, when chemotherapy agents are administered, chemotherapy will be administered first, followed by MLN4924. The infusion of MLN4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced due to toxicities in accordance with Section 6.5. The chemotherapeutic agent may be reduced due to toxicities in accordance with Section 6.5. See Section 6.1 for details of study drug administration. **NOTE: a time-out of approximately 15 minutes is required between end of infusion of chemotherapy regimen and start of infusion of MLN4924.**

d Vital signs are taken immediately before each infusion of docetaxel, paclitaxel, carboplatin, and MLN4924. In addition, vital signs are taken 30 min (± 10 min) after the start of MLN4924 dosing and 1 hr (± 10 min) after completion of MLN4924 dosing. Vital sign measurements will be taken with the

Cycle 2 and Beyond: Arm 1, and Cycle 2 through Cycle 12: Arm 2

Arm 1 (MLN4924 + Docetaxel)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Treatment Cycle (21 Days)[a]						
	Week 1				Week 2	Week 3	
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	Day 8 (± 1 day)	Day 15 (± 1 day)	End of Study[b]

patient in a sitting position.

e A 12-lead ECG will be performed on Day 1 before (within 3 hours) chemotherapy dosing and immediately after the infusion of MLN4924 is complete (± 10 min).

f Hematology samples will be collected before dosing with study drug(s) during Cycle 2 and subsequent cycles on Days 1, 3, and 5; Day 8; Day 15; and at the EOS visit. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

g A coagulation panel at screening (see Schedules of Events: Cycle 1: Arm 1 and Arm 2) will include the following: PT (INR), aPTT, fibrinogen, and D-dimer. If the initial coagulation screen is positive, subsequent coagulation studies should include all of these parameters. If the initial coagulation screen is negative, subsequent coagulation studies should include only PT (INR) and aPTT.

h Clinical chemistry samples will be collected before dosing with study drugs on Days 1, 3, and 5; Day 8; Day 15; and at the EOS visit. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

i Urinalysis samples will be analyzed at the site's local laboratory.

j Urine samples for safety assessments will be collected before any study drug dosing on Day 1 of each new cycle. These samples will be analyzed at a central laboratory.

k All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

l CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter, and at the EOS visit. For each site of disease, the imaging modality (CT or CT and MRI) used at screening must be used throughout the study. CT scans (or MRI) can be taken up to 6 days after the Day 15 visit.

Cycle 13 and Beyond: Arm 2 (as of Amendment 1)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Treatment Cycle (21 Days)[a]				
	Week 1				
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	End of Study[b]
Study Drug Administration					
MLN4924 Infusion[c]	X		X	X	
Paclitaxel + Carboplatin Administration[c]	X				
Procedures					
Symptom-directed Physical Examination	X				X
Weight	X				X
ECOG Performance Status	X				X
Vital Signs[d]	X	X	X	X	X
12-Lead ECG[e]	X	X			
Concomitant Med/Therapy	Recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)				
Hematology[f]	X		X	X	X
Coagulation[g]	X				
Clinical Chemistry Panel[h]	X		X	X	X
Urinalysis with Microscopic Analysis[i]	X		X	X	
SAE Collection[j]	SAEs will be reported from the time informed consent is signed through 30 days (+ 10 days) after the last dose of study drug(s)				

Cycle 13 and Beyond: Arm 2 (as of Amendment 1)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Treatment Cycle (21 Days)[a]				
	Week 1				
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	End of Study[b]
AE Collection[j]	Recorded from the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)				
Tumor Assessment by RECIST (CT/MRI)[k]	To be performed after completion of every sixth cycle after the patient's previous scan				X

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOS=End of Study (visit); INR=international normalized ratio; IV=intravenous(ly); Med=medication; MRI=magnetic resonance imaging; PE=physical examination; PT=prothrombin time; RESIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

a For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to ≤ Grade 1, to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician (Section 6.5).

b The EOS visit will occur 30 days (+ 10 days) after the last dose of study drug(s) or before the start of subsequent therapy for their indication, if that occurs sooner.

c On Day 1, when chemotherapy agents are administered, chemotherapy will be administered first, followed by MLN4924. The infusion of MLN4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced due to toxicities in accordance with Section 6.5. The chemotherapeutic agent may be reduced due to toxicities in accordance with Section 6.5. See Section 6.1 for details of study drug administration. **NOTE: a time-out of approximately 15 minutes is required between end of infusion of chemotherapy regimen and start of infusion of MLN4924.**

d Vital signs are taken immediately before each infusion of drug(s). In addition, vital signs are taken 30 min (± 10 min) after the start of MLN4924 dosing and 1 hr (± 10 min) after completion of MLN4924 dosing. Vital sign measurements will be taken with the patient in a sitting or supine position.

e A 12-lead ECG will be performed on Day 1 before (within 3 hours) chemotherapy dosing and immediately after the infusion of MLN4924 is complete (± 10 min).

f Hematology samples will be collected before dosing with study drug(s) during Cycle 13 and subsequent cycles on Days 1, 3, and 5; and at the EOS visit. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

g A coagulation panel at screening (see Schedules of Events: Cycle 1: Arm 1 and Arm 2) will include the following: PT (INR), aPTT, fibrinogen, and

Cycle 13 and Beyond: Arm 2 (as of Amendment 1)

Arm 2 (Carboplatin Lead-in [MLN4924 + Carboplatin] and MLN4924 + Paclitaxel + Carboplatin)

	Treatment Cycle (21 Days)[a]				
	Week 1				
	Day 1 Predose	Day 1 Postdose	Day 3	Day 5	End of Study[b]

D-dimer. If the initial coagulation screen is positive, subsequent coagulation studies should include all of these parameters. If the initial coagulation screen is negative, subsequent coagulation studies should include only PT (INR) and aPTT.

h Clinical chemistry samples will be collected before dosing with study drugs on Days 1, 3, and 5 and at the EOS visit. On Days 1, 3, and 5, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

i Urinalysis samples will be analyzed at the site's local laboratory.

j All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

k CT scans with IV contrast encompassing the known sites of disease will be performed after completion of every sixth cycle after the patient's previous scan, and at the EOS visit. For each site of disease, the imaging modality (CT or CT and MRI) used at screening must be used throughout the study. CT scans (or MRI) can be taken up to 6 days after the Day 15 visit.

Cycle 1: Arm 3

Arm 3 (MLN4924 + Gemcitabine)

		Treatment Cycle (28 Days)						
		Week 1			Week 2	Week 3	Week 4	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	End of Study[b]
Study Drug Administration								
MLN4924 Infusion[c]		X			X	X		
Gemcitabine Administration[c]		X			X	X		
Procedures								
Informed Consent	X							
Inclusion/Exclusion	X							
Demographics	X							
Complete Medical History	X							
Full Physical Examination	X							X
Symptom-directed Physical Examination		X		X	X	X		
Pregnancy Test (Females of Child-bearing Potential Only)	X							
Height	X							
Weight[d]	X	X[e]						X
ECOG Performance Status	X	X[e]						X
Vital Signs[f]	X	X[e]	X	X	X	X		X
12-Lead ECG[g]	X	X[e]	X					
Concomitant Medications/Therapy		Recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)						

Cycle 1: Arm 3

Arm 3 (MLN4924 + Gemcitabine)

		Treatment Cycle (28 Days)						
		Week 1			Week 2	Week 3	Week 4	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	End of Study[b]
Hematology[h]	X	X[e]		X	X	X	X	X
Coagulation[i]	X	X[e]						
Clinical Chemistry Panel[j]	X	X[e]	X	X	X	X	X	X
Urinalysis With Microscopic Analysis[k]	X	X[e]		X	X	X		
Urine Safety Assessment[l]	X	X		X	X	X		
Echocardiogram	X							
Serious Pretreatment Events and SAE Collection[m]	Serious pretreatment events and SAEs will be reported from the time informed consent is signed through 30 days (+ 10 days) after the last dose of study drug(s)							
AE Collection[m]		Recorded from the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)						
Blood Samples for PK[n]		X	X	X				
Biomarker Blood Samples[o]	X							
Banked Tumor Tissue[p]	X							
Tumor Assessment by RECIST (CT/MRI)[q]	X							

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOS=End of Study (visit); hr=hour(s); INR=international normalized ratio; IV=intravenous(ly); min=minute(s); MRI=magnetic resonance imaging; PE=physical examination; PK=pharmacokinetic; PT=prothrombin time; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

a Screening assessments will be performed within 28 days before the Day 1 dose of study drugs.

b The EOS visit will occur 30 days (+ 10 days) after the last dose of study drugs or before the start of subsequent therapy for their indication, if that occurs

Cycle 1: Arm 3

Arm 3 (MLN4924 + Gemcitabine)

		Treatment Cycle (28 Days)						
		Week 1			Week 2	Week 3	Week 4	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	End of Study[b]

sooner.

c On Days 1, 8, and 15, gemcitabine will be administered first, followed by MLN4924. The infusion of ML4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced due to toxicities in accordance with Section 6.5. The dose of gemcitabine may be reduced due to toxicities in accordance with Section 6.5. See Section 6.1 for details of study drug administration. **Note: a time-out of approximately 15 minutes is required after dosing with gemcitabine and before the start of MLN4924 infusion.**

d Weight should be measured predose.

e Procedures conducted during screening that are performed within 3 days of Day 1 can also be used as the Day 1 predose evaluation and do not need to be repeated.

f Vital signs are taken immediately before each infusion of gemcitabine and MLN4924. In addition, vital signs are taken 30 min (± 10 min) after the start of MLN4924 dosing, and 1 hour (± 10 min) after completion of MLN4924 dosing. On Cycle 1 Day 1, additional vital signs should be obtained 3 hours (± 30 min) after completion of MLN4924 dosing. All of these vital signs are taken with the patient in a sitting position. In addition, at predose and 1 hour postdose of MLN4924 administration on Cycle 1 Day 1, orthostatic blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting for approximately 3 to 4 minutes.

g A 12-lead ECG will be performed during screening and on Day 1 before (within 3 hours) gemcitabine dosing, immediately after the infusion of MLN4924 is complete (± 10 min).

h Hematology samples will be collected during screening; before dosing with study drug(s) on Days 1, 8, and 15; Day 2; Day 22; and at the EOS visit. On Days 1, 8, and 15, samples can be drawn within 24 hours predose. **For dosing Days only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

i A coagulation panel at screening will include the following: PT (INR), aPTT, fibrinogen, and D-dimer. If the initial coagulation screen is positive, follow-up coagulation studies should include all of these parameters. If the initial coagulation screen is negative, follow-up coagulation studies should include only PT (INR) and aPTT.

j Clinical chemistry samples will be collected during screening and before dosing with study drugs on Days 1, 8, and 15. On Days 1, 8, and 15, samples can be drawn within 24 hours predose. In addition, samples will be taken on Day 1 at 3 hours (± 30 min) postinfusion with MLN4924; Day 2; Day 22; and at the EOS visit. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

k Urinalysis samples will be analyzed by the site's local laboratory.

Cycle 1: Arm 3

Arm 3 (MLN4924 + Gemcitabine)

		Treatment Cycle (28 Days)						
		Week 1			Week 2	Week 3	Week 4	
	Screening[a]	Day 1 Predose	Day 1 Postdose	Day 2	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 1 day)	End of Study[b]

l Urine samples for safety assessments will be collected at screening; before any study drug dosing on Days 1, 8, and 15; and on Day 2. These samples will be analyzed at a central laboratory.

m All serious pretreatment events (occurring before the first dose of any study drug) will only be reported to CCI and will not be entered on the eCRF. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

n See the Schedules of Events: refer to Cycle 1: Arm 3 Dose Escalation Pharmacokinetics Schedule during the dose escalation phase of the study, and refer to Cycle 1: Arm 3 MTD Expansion Pharmacokinetics Schedule during the MTD expansion phase of the study.

o Two blood samples will be collected: one to generate a plasma sample and the other to generate genomic DNA for assessment of biomarkers of response.

p A specimen of fixed tumor sample will be collected for genetic characterization of the patient's tumor and for assessment of candidate biomarkers of response to MLN4924-containing therapy. Suitable specimens are either a tumor block or 10 to 20 unstained slides.

q CT scans with IV contrast of the chest, abdomen, and pelvis will be performed during screening. If the sites of disease are not adequately imaged by CT, MRI may also be used to evaluate sites of disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1 Day 1, then the results of those scans may be used for the screening assessment.

Cycle 1: Arm 3 Dose Escalation Pharmacokinetics Schedule

Arm 3 (MLN4924 + Gemcitabine) Dose Escalation Phase: Cycle 1 Timing of Pharmacokinetic Measurements

	Cycle 1				
			After End of MLN4924 Infusion		
	Pre-infusion	End of MLN4924 Infusion	1.5 hour ± 15 min	3 hour ± 30 min	20 hour ± 2 hour
Day 1	X[a]	X[b]	X	X	
Day 2					X[c]

a The sample is to be collected within 1 hour before the start of MLN4924 infusion.

b The sample is to be collected at the end of MLN4924 infusion (immediately before switching off the infusion pump).

c Note that the 20-hour time point after completion of the infusion on Day 1 will actually fall on Day 2.

Cycle 1: Arm 3 MTD Expansion Pharmacokinetics Schedule

Arm 3 (MLN4924 + Gemcitabine) Maximum Tolerated Dose Expansion Phase: Cycle 1 Timing of Pharmacokinetic Measurements

	Cycle 1					
			After End of MLN4924 Infusion			
	Pre-infusion	End of MLN4924 Infusion	1.5 hour ± 15 min	3 hour ± 30 min	7 hour ± 45 min	20 hour ± 2 hour
Day 1	X[a]	X[b]	X	X	X	
Day 2						X[c]

a The sample is to be collected within 1 hour before the start of MLN4924 infusion.
b The sample is to be collected at the end of MLN4924 infusion (immediately before switching off the infusion pump).
c Note that the 20-hour time point after completion of the infusion on Day 1 will actually fall on Day 2.

Cycle 2 and Beyond: Arm 3
Arm 3 (MLN4924 + Gemcitabine)

	Treatment Cycle (28 Days)[a]					
	Week 1		Week 2	Week 3	Week 4	
	Day 1 Predose	Day 1 Postdose	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 4 days)	End of Study[b]
Study Drug Administration						
MLN4924 Infusion[c]	X		X	X		
Gemcitabine Administration[c]	X		X	X		
Procedures						
Full Physical Examination	X					X
Symptom-directed Physical Examination			X	X		
Weight	X					X
ECOG Performance Status	X					X
Vital Signs[d]	X	X	X	X		X
12-Lead ECG[e]	X	X				
Concomitant Med/Therapy	Recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)					
Hematology[f]	X		X	X	X	X
Coagulation[g]	X					
Clinical Chemistry Panel[h]	X		X	X	X	X
Urinalysis with Microscopic Analysis[i]	X					
Urine Safety Assessments[j]	X					

Cycle 2 and Beyond: Arm 3
Arm 3 (MLN4924 + Gemcitabine)

	Treatment Cycle (28 Days)[a]					
	Week 1		Week 2	Week 3	Week 4	
	Day 1 Predose	Day 1 Postdose	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 4 days)	End of Study[b]
SAE Collection[k]	SAEs will be reported from the time informed consent is signed through 30 days (+ 10 days) after the last dose of study drug(s)					
AE Collection[k]	Recorded from the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s)					
Tumor Assessment by RECIST (CT/MRI)[l]					X	X

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOS=End of Study (visit); INR=international normalized ratio; IV=intravenous(ly); Med=medication; MRI=magnetic resonance imaging; PE=physical examination; PT=prothrombin time; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event.

a For a new cycle of treatment with study drugs to begin, toxicities considered to be related to treatment with study drugs must have resolved to ≤ Grade 1, to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician (Section 6.5).

b The EOS visit will occur 30 days (+ 10 days) after the last dose of study drug(s) or before the start of subsequent therapy for their indication, if that occurs sooner.

c The infusion of MLN4924 may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of MLN4924 may be reduced due to toxicities in accordance with Section 6.5. The dose of gemcitabine may be reduced due to toxicities in accordance with Section 6.5. See Section 6.1 for details of study drug administration. **Note: a time-out of approximately 15 minutes is required after dosing with gemcitabine and before the start of MLN4924 infusion**.

d Vital signs are taken immediately before infusion of gemcitabine and MLN4924. In addition, vital signs are taken 30 min (± 10 min) after the start of MLN4924 dosing and 1 hr (± 10 min) after completion of MLN4924 dosing. Vital sign measurements will be taken with the patient in a sitting position.

e A 12-lead ECG will be performed on Day 1 before (within 3 hours) gemcitabine dosing and immediately after the infusion of MLN4924 is complete (± 10 min).

f Hematology samples will be collected before dosing with study drug(s) during Cycle 2 and all subsequent cycles on Days 1, 8, 15; Day 22; and at the EOS visit. On Days 1, 8, and 15, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

g A coagulation panel at screening (see Schedules of Events: Cycle 1: Arm 3) will include the following: PT (INR), aPTT, fibrinogen, and D-dimer. If the initial coagulation screen is positive, subsequent coagulation studies should include all of these parameters. If the initial coagulation screen is negative,

Cycle 2 and Beyond: Arm 3
Arm 3 (MLN4924 + Gemcitabine)

	Treatment Cycle (28 Days)[a]					
	Week 1		Week 2	Week 3	Week 4	
	Day 1 Predose	Day 1 Postdose	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 22 (± 4 days)	End of Study[b]

subsequent coagulation studies should include only PT (INR) and aPTT.

h Clinical chemistry samples will be collected before dosing with study drugs on Days 1, 8, and 15; Day 22; and at the EOS visit. On Days 1, 8, and 15, samples can be drawn within 24 hours predose. **For Day 1 dosing only:** if dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.

i Urinalysis samples will be analyzed at the site's local laboratory.

j Urine samples for safety assessments will be collected before any study drug dosing on Day 1 of each new cycle. These samples will be analyzed at a central laboratory.

k All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

l CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter, and at the EOS visit. For each site of disease, the imaging modality (CT or CT and MRI) used at screening must be used throughout the study. CT scans (or MRI) can be taken up to 6 days after the Day 22 visit.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
a fib	atrial fibrillation
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}24\ hr}$	AUC from time zero to 24 hours
BCRP	breast cancer resistance protein
BID	*bis in die*; twice a day
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BSA	body surface area
BUN	blood urea nitrogen
CDL	cullin-dependent ubiquitin E3 ligases
Cdt-1	chromatin-licensing and DNA-replication factor-1
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
Cri	incomplete blood count recovery
CRM	continual reassessment method
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P_{450}
DCSI	Development Core Safety Information
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Term
EOS	End of Study (visit)
CCI	[redacted]
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GI	Gastrointestinal
HCT	human colon tumor
HIV	human immunodeficiency virus
hr	hour(s)
HUS	hemolytic uremic syndrome
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IP	intraperitoneally
IRB	institutional review board
IV	intravenous; intravenously
LDH	lactate dehydrogenase
LFT	liver function test(s)
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndromes
Med	medication
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
min	minute(s)
MRI	magnetic resonance imaging
MRP2	multidrug resistance associated protein 2
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCIC CTG	National Cancer Institute of Canada Clinical Trials Group
NEDD8	neural precursor cell expressed developmentally down-regulated protein 8
NF-κB	nuclear (transcription) factor-kappa B
Nrf2	NFE2-related factor 2
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OATP	organic anion-transporting polypeptides

Abbreviation	Term
PD	progressive disease (disease progression)
PE	physical exam
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PMTD	predicted maximum tolerated dose
PR	partial response
PS	performance status
PT	prothrombin time
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	every week
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCLC	small cell lung cancer
SD	stable disease
SoC	standard of care
SWOG	Southwest Oncology Group
T/C	ratio of tumor volume of treated vs control group
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Study Drug

MLN4924 is a first-in-class small molecule inhibitor of the neural precursor cell expressed developmentally down-regulated protein 8 (NEDD8)-activating enzyme (NAE) that is being developed for the treatment of malignancies. NAE is an essential component of the NEDD8 conjugation pathway, which controls the activity of a subset of ubiquitin E3 ligases, multiprotein complexes that transfer ubiquitin molecules to protein substrates that are then targeted to the proteasome for degradation. Cullin-dependent ubiquitin E3 ligases (CDLs) require conjugation to NEDD8 to be activated. CDLs control the timely ubiquitination and consequent proteasomal degradation of proteins with important roles in cell cycle progression and signal transduction, cellular processes that are integral to tumor cell growth, proliferation, and survival. Inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by disrupting proteasomal degradation of a variety of critical regulatory proteins.

1.2 Nonclinical Experience

1.2.1 Single-Agent MLN4924

MLN4924 is a potent and selective inhibitor of NAE activity. It is approximately 300-fold and 1800-fold more selective for NAE over the close family members, ubiquitin-activating enzyme and sumo-activating enzyme, respectively.[2] Moreover, MLN4924 is selective for NAE when compared to kinases and adenosine receptors.[2]

MLN4924 treatment of cultured tumor cells resulted in changes in protein levels consistent with the inhibition of NAE, in particular a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including NFE2-related factor 2 (Nrf2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE inhibition by MLN4924 led to deoxyribonucleic acid (DNA) re-replication and accumulation of cells in the S-phase of the cell cycle; this resulted in DNA damage and subsequent cell death through apoptosis.[2, 3, 4] An exception to this was the OCI Ly10 lymphoma cell line that is dependent on nuclear (transcription) factor-kappa B (NF-κB) activity for survival.[5] In this line, NAE inhibition led to an accumulation of cells at the G1 phase of the cell cycle that was followed by cell death through apoptosis, suggesting that

there may be multiple consequences of NAE inhibition that lead to cell death, depending on the genetic background of the malignant cells.

MLN4924 treatment inhibited the growth of a wide variety of solid tumor cell lines, with concentration producing 50% inhibition (IC_{50}) < 200 nM in 2 or more bladder, brain, breast, cervix, colon, liver, lung, melanoma, prostate, ovary, sarcoma, and uterine cancer cell lines among a panel of 240 cell lines evaluated (Ricerca panel report, data on file). Analysis of an independent experiment investigating the sensitivity of a panel of 653 cell lines of various histologies to MLN4924 indicated that some histologies were on average more sensitive than others; the most sensitive histologies included bladder, squamous cell lung, esophageal, and head and neck squamous cell cancer (Massachusetts General Hospital panel analysis, data on file).

MLN4924 demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and acute myelogenous leukemia (AML) xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. For example, treatment of mice bearing SC HCT116 tumor xenografts with a single SC dose of MLN4924 resulted in dose-dependent inhibition of NEDD8-cullin levels and stabilization of CDL substrates including Nrf2 and Cdt-1.[(2)] MLN4924 showed significant single-agent antitumor activity in solid tumor xenograft models derived from colon (HCT116[(2)] and HT29 [Millennium Pharmaceuticals, Inc., and its affiliates (Millennium) data on file]), non-small cell lung cancer (NSCLC) (Calu-6 and H522)[(2)], small cell lung cancer (SCLC) (NCI-H82 and NCI-H69 [Millennium data on file]), melanoma (PHTX50M),[(6)] breast (PHTX02B [Millennium data on file]), and esophageal cancer (ESM199 and ESM204 [Millennium data on file]). Despite antitumor activity in this wide variety of xenograft models, very few of the solid tumor models underwent complete regressions in response to MLN4924, and MLN4924 demonstrated limited single-agent activity in other xenograft models derived from these same types of cancer, such as the esophageal model ESM026 (Millennium data on file) and melanoma models including SK-MEL-24 and 1205Lu.[(7)]

Detailed information regarding the nonclinical pharmacology and toxicology of MLN4924 may be found in the Investigator's Brochure (IB).

1.2.1.1 Nonclinical Pharmacology: Nonclinical Studies With MLN4924 in Combination With Agents Employed in Current Solid Tumor Clinical Practice

The observations of single-agent activity of MLN4924 described in Section 1.2.1 provided the rationale for evaluating MLN4924 in combination with standard anticancer agents to improve antitumor activity in nonclinical studies. Agents were selected for nonclinical testing based on several criteria: 1) their clinical use in tumor types showing highest sensitivity to MLN4924 in cell line screens described in Section 1.2.1 (for example, docetaxel is widely used to treat squamous NSCLC and esophageal cancer), and 2) consideration of the DNA re-replication/DNA damage phenotype induced by MLN4924 and the possibility of enhancing this effect with another agent that affects DNA replication (ie, gemcitabine) or causes DNA damage (ie, platinum-based drugs). NAE inhibition with MLN4924 has been shown to dysregulate multiple aspects of the DNA damage response, including the p53 pathway, the breast cancer susceptibility gene 1 (*BRCA1*)/breast cancer susceptibility gene 2 (*BRCA2*) complex, transcription-coupled nucleotide excision repair, and base excision repair.[8] When functional, these DNA repair pathways can limit the extent of the damage caused by chemotherapeutic agents such as platins; therefore, the inhibition of the repair pathways by MLN4924 may sensitize cells to DNA damaging effects of chemotherapeutic agents.

In vitro and in vivo nonclinical studies were conducted to assess antitumor activity of MLN4924 in combination with selected standard of care (SoC) agents and to determine whether MLN4924 showed additive or synergistic antitumor activity with these combination agents, which could support the clinical evaluation of the combinations. In vitro experiments used 4 cell lines (HCT116 colorectal carcinoma, A375 melanoma, U2OS osteosarcoma, and A549 NSCLC) to test the combination of MLN4924 with widely-used chemotherapy agents. In vivo experiments used xenograft models derived from cancer types in which the SoC agents are used in clinical practice. These included 2 derived from SCLC cell lines (NCI-H69 and NCI-H82) for evaluation with platinum-based drugs, 1 derived from a NSCLC cell line (NCI-H1650) for evaluation with docetaxel, and a primary human xenograft tumor model derived from a triple-negative breast cancer patient (PHTX02B) for evaluation with docetaxel and with gemcitabine. The nonclinical studies described below provide evidence of in vitro and/or in vivo combination benefit with taxanes, platins, and gemcitabine, and support the planned clinical investigation of the tolerability of these agents in combination with MLN4924 (Millennium data on file). Nonclinical combination studies

in additional xenograft models are ongoing, as are mechanistic studies to understand the basis for combination effects in vitro.

1.2.2 MLN4924 in Combination With Taxane-based Therapy

MLN4924 and docetaxel exhibited additive antitumor activity in multiple in vitro and in vivo models. In particular, docetaxel and MLN4924 showed an additive effect in vitro in the HCT116 colorectal carcinoma, A375 melanoma, U2OS osteosarcoma, and A549 NSCLC cell lines with simultaneous addition of compounds. To determine whether the combination effect was influenced by the order and timing of compound addition, A549 cells were treated with MLN4924 for 8, 24, or 48 hours before docetaxel treatment, and conversely, cells were treated with docetaxel for 8, 24, or 48 hours before MLN4924 treatment. The combination was additive under all of these conditions, suggesting that within a 48-hour time frame, the order of compound addition did not alter the combination effect.

The combination of MLN4924 and docetaxel was evaluated in vivo in NCI-H1650 NSCLC xenograft-bearing mice and in PHTX02B primary human breast cancer xenograft-bearing mice and showed additive antitumor activity in both xenograft models compared to single-agent treatment with either MLN4924 or docetaxel alone. In the PHTX02B model, treatment with a combination of MLN4924 (60 mg/kg SC twice daily [BID] 5 days on/5 days off) and docetaxel (5 mg/kg intravenously [IV] every week [QW]) resulted in tumor regression or complete inhibition of tumor growth (ratio of tumor volume of treated vs control group [T/C] on Day 21=0.05), whereas treatment with the individual agents at these dose levels and schedules resulted in only partial tumor growth inhibition (T/C=0.26 and 0.36 for MLN4924 and docetaxel, respectively). A pharmacodynamic study was conducted in the PHTX02B model to evaluate the level of cleaved caspase-3 (a marker of apoptosis) induced by MLN4924, docetaxel, or the combination of MLN4924 and docetaxel. Levels of cleaved caspase-3 in xenograft tumors from the MLN4924 and docetaxel combination group were higher than those in the single-agent groups, indicating that the combination resulted in enhanced apoptosis. This nonclinical evidence of improved antitumor activity of MLN4924 administered in combination with docetaxel supports further evaluation of taxane combinations with MLN4924 in the clinic.

1.2.3 MLN4924 in Combination With Platinum-based Therapy

MLN4924 and platinum-based drugs exhibited synergistic antitumor activity in multiple in vitro and in vivo models. The in vitro combination of MLN4924 and cisplatin demonstrated synergy in HCT116, A549, and U2OS cell lines and additivity in the A375 cell line.

The combination of MLN4924 with carboplatin was evaluated in vivo in NCI-H69 SCLC xenograft-bearing mice and showed synergistic antitumor activity compared to treatment with either MLN4924 or carboplatin alone. The combination of MLN4924 (120 mg/kg SC BID Days 1, 4, 8, 11, 15, and 18) and carboplatin (50 mg/kg intraperitoneally [IP] QW) resulted in tumor stasis or regression (T/C=0.10), while treatment with either MLN4924 or carboplatin alone resulted in only partial tumor growth inhibition (T/C=0.44 and 0.53, respectively). Synergistic activity was also demonstrated using carboplatin at 50 mg/kg IP QW in combination with a lower dose of MLN4924 (60 mg/kg SC BID Days 1, 4, 8, 11, 15, and 18). Combination of MLN4924 with cisplatin showed additive and synergistic effects in the NCI-H69 and NCI-H82 SCLC xenograft models using 2 schedules of MLN4924 (Days 1, 3, and 5 QW or Days 1 and 4 each week for 3 weeks) with 4 mg/kg of cisplatin dosed IP on Days 1, 5, and 9. Taken together, these nonclinical results demonstrate the benefit of MLN4924 in combination with platinum-based chemotherapy. Preliminary studies suggest that the ability of MLN4924 to inhibit the nucleotide excision repair pathway contributes to its synergy with platinum-based drugs; additional nonclinical studies are ongoing to further investigate the mechanism of synergy.

1.2.4 MLN4924 in Combination With Gemcitabine

MLN4924 and gemcitabine demonstrated a combination benefit in vitro and in vivo. The combination of MLN4924 and gemcitabine in vitro showed synergistic effects in HCT116 and U2OS cell lines, but the compounds demonstrated subadditive effects in the A375 melanoma and A549 NSCLC cell lines. The combination of MLN4924 with gemcitabine was evaluated in PHTX02B xenograft-bearing mice and showed additive antitumor activity compared to treatment with either MLN4924 or gemcitabine alone. Treatment with a combination of MLN4924 (30 mg/kg SC BID for 21 days) and gemcitabine (10 mg/kg IP dosed on Days 1, 4, 7, and 10) resulted in tumor stasis (T/C=0.12), whereas treatment with either MLN4924 or gemcitabine alone resulted in only partial tumor growth inhibition (T/C=0.39 and 0.46, respectively). Taken together, these results support the further investigation of MLN4924 in combination with gemcitabine in patients. Additional nonclinical work is planned to understand the mechanism of synergy in selected cell lines in vitro and to evaluate the combination in additional in vivo models, particularly of pancreatic cancer.

1.3 Clinical Experience

Single-agent MLN4924 has been studied in phase 1 clinical trials in patients with advanced nonhematologic malignancies (Study C15001); lymphoma and multiple myeloma

(Study C15002); AML, myelodysplastic syndromes (MDS), or acute lymphoblastic leukemia (ALL) (Study C15003); and melanoma (Study C15005). These are all single-agent, dose escalation studies. Based on information available as of 22 January 2013, a total of 220 patients have been enrolled into these studies, and safety data are available and summarized for 217 of these patients (ie, those included in the safety population).

MLN4924 is administered as a 1-hour IV infusion in these protocols. Six dosing schedules using a 21-day cycle were assessed across these studies (dosing on Days 1-5; Days 1, 3, and 5; Days 1 and 8; Days 1, 2, 8, and 9; Days 1, 8, and 15; and Days 1, 4, 8, and 11) in a coordinated fashion.

Study C15001 began in April 2008, and 62 patients with solid tumors have been enrolled. The median age of the patients included in the safety population is 59.5 years, ranging from 34 to 84 years. One patient (a 45-year-old man with metastatic melanoma and bone and lung involvement) had a partial response (PR) on Schedule A at a dose of 25 mg/m^2. In addition, 10 patients with the following solid tumors remained on treatment for at least 5 cycles and all achieved a best response of stable disease (SD) that lasted for up to 10 cycles: colorectal carcinoma and melanoma (3 each), breast cancer (2), and SCLC and head and neck cancer (1 each). This study has been completed, and the database was locked on 06 December 2012.

Study C15002 began in June 2008, and 53 patients with multiple myeloma (21) or lymphoma (32) have been enrolled. The median age of the patients included in the safety population is 60.0 years, ranging from 26 to 91 years. Three PRs have been observed in this study at doses of 110 to 196 mg/m^2: 1 patient each with diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma, and peripheral T-cell lymphoma. The patient with DLBCL achieved PR in Cycle 3, and the duration of this response was 158 days. Patient enrollment in the dose expansion cohorts was ongoing as of 22 January 2013.

Study C15003 is an ongoing, phase 1 study evaluating patients with AML (patients with MDS and ALL are also evaluated) using single-agent MLN4924. As of 22 January 2013, 68 patients have been enrolled in this study, which was designed to test several 21-day dose schedules. For Schedule A (Days 1, 3, and 5), 4 dose levels have been determined safe: 25, 33, 44, and 59 mg/m^2. The maximum tolerated dose (MTD) for Schedule A was established at 59 mg/m^2 based on a dose-limiting toxicity (DLT) of increased transaminases observed at a dose level of 78 mg/m^2. Enrollment in Schedule B (Days 1, 4, 8, and 11) was de-escalated to 110 mg/m^2 based on 2 serious adverse events (SAEs) for patients dosed at 147 mg/m^2:

1 fatal (acute renal failure) and 1 life threatening (cardiac failure). The dose was subsequently reduced to 83 mg/m^2 to further enhance the safety margin. Schedule C (Days 1, 8, and 15) was tested in 2 patients (both received only 1 cycle of treatment), and Schedule D (Days 1, 4, 8, and 11 in combination with azacitidine) was tested in only 1 patient (although the patient received only MLN4924). Nine patients enrolled in a new expansion cohort, Schedule E, which was added to this protocol to further evaluate the dosing schedule of MLN4924 on Days 1, 3, and 5 at a fixed dose of 50 mg/m^2.

There have been 7 responses in Study C15003, including complete responses (CRs). Four responses occurred in the first 27 patients treated on the Days 1, 3, and 5 schedule at 25 mg/m^2, 33 mg/m^2, 44 mg/m^2, and 59 mg/m^2 and are further described below. Two PRs (in the next 26 patients treated) occurred on the Days 1, 4, 8, and 11 schedule, both at 83 mg/m^2. Four of the 6 responders remained on study drug for 8, 12, 13, and 19 cycles, respectively. One response occurred on the Days 1, 3, and 5 schedule (Schedule E) at 50 mg/m^2.

The following patients had responses on the Days 1, 3, and 5 schedule:

- A 29-year-old woman with relapsed (French-American-British subtype M4) acute AML (with isolated trisomy 8) following allogeneic stem cell transplantation achieved complete remission after Cycle 1 treatment with 25 mg/m^2 MLN4924. Her cytogenetic complete remission continued before she experienced extramedullary disease progression in Cycle 8. Prior treatments included "7 and 3" induction therapy followed by high-dose cytarabine and then allogeneic bone marrow transplantation.

- A 51-year-old man with refractory AML following allogeneic stem cell transplantation achieved a marrow complete remission with incomplete blood count recovery (CRi) after Cycle 1 at 59 mg/m^2. This patient also had extramedullary disease (awaiting restaging). He received 2 doses of study drug in Cycle 2 before dying of an intracranial hemorrhage resulting from a fall.

- A 71-year-old man with de novo AML refractory to standard cytarabine plus daunorubicin induction achieved a CRi during Cycle 1 at 44 mg/m^2. Although this response was not maintained, the patient continued to benefit from MLN4924 treatment, which was subsequently escalated to 59 mg/m^2. The patient was taken off study after completing 19 cycles. He was hospitalized with pneumonia and subsequently died of sepsis.

- An 82-year-old man with high-risk, azacitidine-refractory MDS that had evolved into AML before receiving study drug had a partial remission in Cycle 8, a CRi in Cycle 10 (at 33 mg/m^2), and became transfusion-independent before progressing after Cycle 12.

- A 73-year-old woman with de novo AML had a PR on Schedule E at 50 mg/m^2.

Study C15005 began in December 2009, and 37 patients with melanoma have been enrolled. The median age of the patients in the safety population is 61.8 years, ranging from 33 to 79 years. Six patients stayed on the study for at least 5 cycles and achieved a best response of SD, and 1 patient achieved a PR. This study has been completed, and the clinical database was locked on 06 December 2012. Additional information on the clinical experience with MLN4924 in patients with solid tumors is provided in Section 1.4.3.

Overall, the intermittent schedule of drug administration was better tolerated than the daily schedule. Based on the observation that doses of MLN4924 equal to or above 110 mg/m^2 were associated with an increased frequency of Cycle 1 Day 1 SAEs, patients enrolled across phase 1 studies were to receive MLN4924 at doses equal to or below 100 mg/m^2. A maximum dose of 50 mg/m^2 was selected for Arms 1 and 2 (both on the Days 1, 3, and 5 schedule), and 100 mg/m^2 was selected for Arms 3 (Days 1, 8, and 15) in this study (see Section 1.4.3 for additional information).

The pharmacokinetics (PK) of MLN4924 following single and multiple IV administrations have been evaluated based on preliminary data from these phase 1 studies. Plasma concentrations of MLN4924 declined in a multi-exponential manner at the end of a 1-hour IV infusion, with little or no notable drug accumulation following once-daily dosing for 5 consecutive days or more intermittent dosing. This observation is consistent with a mean terminal elimination half-life of approximately 5 to 8 hours estimated across doses and schedules. MLN4924 PK is linear over the dose range studied based on a daily area under the plasma concentration versus time curve from time zero to 24 hours ($AUC_{0\text{-}24hr}$) that increased proportionately with dose from 25 to 261 mg/m^2; single dose maximum (peak) concentration (C_{max}; theoretically end-of-infusion concentration) appeared to increase slightly more than dose proportionally at the highest doses (fewer observations available). MLN4924 systemic clearance and volume of distribution appear to increase with increasing body size (body surface area [BSA] range 1.48-2.72 m^2), supporting BSA-normalized dosing to reduce variation in systemic exposure.

Preliminary pharmacodynamic analyses in both hematologic and nonhematologic indications demonstrate target and downstream pathway inhibition following MLN4924 dosing at all doses tested in tumor and surrogate tissues. MLN4924-NEDD8 adduct is a unique molecular species formed as a consequence of the intracellular interaction of NAE with MLN4924 and NEDD8, and is indicative of MLN4924 inhibition of NAE.[9] MLN4924-NEDD8 adduct was detected by immunohistochemistry in postdose but not predose solid tumor biopsies in 11/11 patients demonstrating target inhibition 3 to 6 hours following MLN4924 dosing in all cases (dose range 50-83 mg/m^2). In addition, changes in CDL substrates Cdt-1 and Nrf2 were investigated in predose and postdose skin and tumor biopsies, with the majority of patients demonstrating postdose increases (1.5- to 25-fold) in Cdt-1 and/or Nrf2 in skin (27/34 patients) or tumor (9/11). In addition, pharmacodynamic assessments of MLN4924-adduct and Cdt-1 in predose and postdose bone marrow aspirates obtained from patients with AML or high grade MDS indicate target and pathway inhibition throughout the dose range tested (25-78 mg/m^2). Additional information on safety, PK, and pharmacodynamics is provided in the IB.

The risks of MLN4924 treatment, based on preliminary findings from the clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, are presented in Section 1.5.1.

1.4 Study Rationale

MLN4924 demonstrated broad-based antitumor activity in a variety of cell lines of solid tumor origin including squamous cell lung cancer, small cell lung cancer, head and neck squamous cell carcinoma, esophageal cancer, and bladder cancer. In vivo data support combinations including taxane-based treatments, gemcitabine, and platinum-based treatments.

Clinical experience with single-agent MLN4924 demonstrated potential activity in a variety of solid tumor malignancies in 2 phase 1 studies: C15001 (all solid tumors, N=62) and C15005 (melanoma, N=37). Despite treatment failure on multiple lines of prior therapy, a number of these patients benefited from treatment with single-agent MLN4924 as evidenced by durable stable disease (5 cycles or higher), including colorectal carcinoma (3), breast cancer (2), SCLC and head and neck cancer (1 each), and melanoma (9). Two patients with melanoma achieved PR.

Based on the broad-based nonclinical antitumor activity of MLN4924 discussed above, and additive/synergistic antitumor preclinical activity of MLN4924 when combined with

chemotherapeutic agents, the present study was designed to assess the combination of MLN4924 plus docetaxel, paclitaxel + carboplatin, and gemcitabine.

1.4.1 Antitumor Activity of MLN4924 in Solid Tumors

MLN4924 has been investigated as a single agent in solid tumors in 2 phase 1 studies: C15001 was carried out in patients with any solid tumors for whom prior therapies had failed, and C15005 study was carried out in melanoma patients relapsed/refractory to prior therapies. These studies were designed to determine safe and tolerable doses of MLN4924 in various solid tumors and establish a safety database for the molecule. The antitumor activity of MLN4924 as a single agent was also investigated in these studies. Overall, a total of 99 patients with various solid tumors have been treated in these 2 phase 1 studies.

In Study C15001, 10 patients with the following solid tumors stayed on the study for at least 5 cycles: colorectal carcinoma and melanoma (3 each); breast cancer (2); and SCLC, and head and neck cancer (1 each).

Among 20 evaluable patients with melanoma in Study C15005, the disease control rate, defined as the proportion of patients achieving SD or better at first restaging, was 50% (10/20); 6 patients stayed on the study for at least 5 cycles. One 60-year-old woman with wild type-BRAF disease who progressed through multiple (> 6) prior therapies achieved a PR at Cycle 4. She was treated at the 209 mg/m^2 dose level of MLN4924.

The results of these studies indicate potential antitumor activity of MLN4924 in a variety of solid tumors in patients who have been heavily treated with multiple lines of prior therapy, and who are typically very difficult to treat.

The current study builds on nonclinical data demonstrating sensitivity to MLN4924 in certain types of malignancies such as colon, NSCLC, SCLC, melanoma, breast, and esophageal cancer and its augmentation by standard chemotherapy agents (see Section 1.2), limited clinical data as described above, and the strength of published data with well-established chemotherapies used in various malignancies.

1.4.2 Chemotherapy Regimens for Solid Tumors

Three chemotherapy regimens (docetaxel, paclitaxel + carboplatin, and gemcitabine) will be used in this study as combination partners with MLN4924. These regimens have been approved and are considered SoC therapies for various malignancies in front line or relapsed/refractory settings.

Docetaxel is indicated as a single agent for locally advanced or metastatic breast cancer and for locally advanced or metastatic NSCLC after platinum therapy failure.

Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Paclitaxel is also indicated for the second-line treatment of acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma. In addition, paclitaxel in combination with cisplatin is indicated for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents (one established combination regimen consists of carboplatin and cyclophosphamide). Carboplatin is also indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

Gemcitabine is indicated for pancreatic cancer as a single agent.

Docetaxel, paclitaxel, carboplatin, and gemcitabine are also approved in combination with other chemotherapeutic agents to treat other indications; refer to package inserts for additional information.

In addition to the approved indications outlined above, these agents are widely used in a variety of malignancies in patients for whom prior therapies have failed. Paclitaxel/ carboplatin is also widely used for treatment of newly diagnosed NSCLC.

For a detailed description of each of these medications, please see Section 6.12. The choice of the above chemotherapy agents in combination with MLN4924 in this study is based on the following considerations:

- These agents have been well recognized as SoC in a number of malignancies in front-line (carboplatin + paclitaxel) or in various relapse settings (all 3 regimens).
- Their safety profiles, risks, and benefits have been widely studied and reported.
- Additive/synergistic effect of these agents in combination with MLN4924 has been studied in a number of in vitro and in vivo models in house.

Therefore, it is thought that the above SoCs would serve as reasonable partners in combination with MLN4924 for investigations in patients with various solid tumors in this study.

1.4.3 Rationale for Dose and Schedule

No clinical data are currently available for treatment with MLN4924 in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine. Each study arm will aim to establish the MTD of MLN4924 in combination with these agents. As such, MLN4924 in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine will be administered to an initial 3 patients at the lowest planned dose using a modified form of the Bayesian continual reassessment method first proposed by O'Quigley et al[10] (herein referred to as the CRM). The predicted MTD (PMTD) from the CRM model will be updated based on all observed DLTs (Section 6.3). Subsequent escalation, expansion, or de-escalation will be determined as described in Section 6.4. Once at least 6 patients are treated at any dose level and the algorithm does not recommend escalation or de-escalation, this dose level may be considered the MTD of MLN4924 in combination with the SoC.

1.4.3.1 Rationale for Dose and Schedule for Treatment With MLN4924

In previous phase 1 studies, MLN4924 has been tested in various dosing schedules and at doses ranging from 25 to 278 mg/m^2. Pharmacodynamic assessments have demonstrated NAE pathway inhibition at all dose levels tested, including 25 mg/m^2, the lowest dose tested.

To ensure exposure to both MLN4924 and chemotherapy partners and to potentially leverage their mechanisms of action, 2 dosing schedules will be used in this study: for Arm 1 (docetaxel + MLN4924) and Arm 2 (paclitaxel + carboplatin + MLN4924), where chemotherapy regimens are given on Day 1 of each cycle, MLN4924 will be administered on Days 1, 3, and 5 of each cycle, whereas for Arm 3, both MLN4924 and gemcitabine will be administered on Days 1, 8, and 15.

The choice of MLN4924 doses was based on data from single-agent phase 1 studies. For Arms 1 and 2, MLN4924 will be given as a 1-hour IV infusion on Days 1, 3, and 5 of 21-day cycle based on its acceptable safety profile. The planned doses are 15, 25, 37, and 50 mg/m^2. The maximum dose of 50 mg/m^2 was selected because 50 mg/m^2 was the lowest of the currently established MTDs for this schedule. The relevant MTDs included 50 mg/m^2 in Study C15001 Schedule B; 67 mg/m^2 in Study C15001 Schedule C; and 59 mg/m^2 in

Study C15003 Schedule A; see the IB for additional details. Additionally, SAEs for patients receiving treatment on Cycle 1 Day 1 are less likely to occur at doses equal to or below 50 mg/m^2 given that higher doses have been associated with an increased safety risk (see Section 1.5.1). Dosing cycles for both Arm 1 and Arm 2 will last for 21 days.

For Arms 1 and 2 where MLN4924 is given on Days 1, 3, and 5, a starting dose of 15 mg/m^2 was chosen, which is 1 dose level below the lowest dose (25 mg/m^2) tested as a single agent to provide a wider margin of safety. The maximum dose of MLN4924 for Arms 1 and 2 will be 50 mg/m^2.

Because gemcitabine is normally given on Days 1, 8, and 15, in Arm 3, MLN4924 will be administered on the same dosing schedule to ensure that patients are exposed to both drugs on all the dosing days and to leverage the mechanism of action. In Arm 3, MLN4924 will be given as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day cycle. This dosing schedule has been studied in C15001 (solid tumor study), and the MTD was established at 196 mg/m^2. However, based on the observation that doses of IV MLN4924 ≥ 110 mg/m^2 are associated with more severe adverse events (AEs) (see Section 1.5.1), patients will be dosed up to a maximum of 100 mg/m^2. The planned doses are 25, 50, 75, and 100 mg/m^2.

The likelihood of a clinically relevant PK interaction between MLN4924 and the selected SoC regimens is considered to be low. While the metabolic and disposition profiles of MLN4924 remained to be fully characterized in humans, the potential for drug interaction was assessed based on the available nonclinical and clinical data. MLN4924 is metabolized in vitro via hydroxylation oxidation, predominantly by cytochrome P450 (CYP) 3A4 with a small contribution from CYP2D6. Also, MLN4924 neither inhibits nor induces the activity of the 5 major CYPs. In rats and primates, urinary excretion of unchanged MLN4924 was found to be low (< 5%). In vitro studies with efflux pump inhibitors demonstrated that MLN4924 is a substrate for P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein 2 (MRP2). However, MLN4924 is a weak inhibitor of P-gp (IC_{50} [paclitaxel and digoxin] of 41.2-56.0 mM) and BCRP (IC_{50} [estrone-3-sulfate] of 6.3 mM) and is not likely to inhibit MRP2 (IC_{50} > 200 mM). Additional studies with organic anion-transporting polypeptides (OATP) in sandwich-cultured human hepatocytes showed that MLN4924 can inhibit the hepatic uptake of estrone-3-sulfate (IC_{50} of 29.1 mM) as well as of simvastatin (IC_{50} of 0.4-4.9 mM) and lovastatin (IC_{50} of 0.9 mM) from some, but not all, donors. Taking these data together and based on observed C_{max} values at doses ≤ 110 mg/m^2, MLN4924 is unlikely to affect the PK

of other drugs that are known CYP or P-gp substrates, whereas the potential exists, albeit low, for drug interactions with BCRP and OATP substrates at clinical concentrations.

Hepatic metabolism is the major route of elimination of paclitaxel (mainly by CYP2C8 and to a lesser extent CYP3A4) and docetaxel (mainly by CYP3A4/5 and glutathione S-transferase); both of these agents are also substrates for the efflux (P-gp and/or MRP2) and uptake (OATP1B) transporters.[11, 12] Gemcitabine is a prodrug phosphorylated intracellularly to gemcitabine triphosphate by nucleoside kinases; more than 90% of a gemcitabine dose is metabolized by cytidine deaminase and within 1 week, gemcitabine and its inactive uracil metabolite (dFdU) are excreted almost entirely in the urine.[13] Carboplatin is primarily eliminated unchanged via urinary excretion. While some overlap in the metabolizing enzymes and/or transporter proteins involved in the drug clearances exists with MLN4924, more importantly, none of these agents is a known inhibitor or inducer of CYP3A4 (or CPY2D6) in human liver microsomes.

In this study, limited (sparse) PK sampling for determination of MLN4924 plasma concentration will be performed during Cycle 1 of treatment to contribute to a population PK analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine. During the dose escalation portion of the study, PK samples will be obtained on Cycle 1 Day 1 before and after the start of the MLN4924 infusion when MLN4924 is administered for the first time in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine. During the MTD expansion portion of the study, and as permitted by the administration schedule of the combination therapy of MLN4924 with docetaxel or paclitaxel + carboplatin, PK samples will be collected on Cycle 1 Day 1 (MLN4924 + SoC) and Cycle 1 Day 5 (MLN4924 alone) before and after the start of the MLN4924 infusion to assess for possible changes in MLN4924 exposures at a tolerated dose of the combination therapy.

1.4.3.2 Dose and Schedule for Treatment With Docetaxel (Plus MLN4924, Arm 1)

In the dose escalation phase, docetaxel will be administered by IV infusion over 60 minutes at a dose of 75 mg/m^2 in combination with IV MLN4924 doses. Once the MTD of MLN4924 + docetaxel is reached, approximately 6 additional patients will be enrolled for a total of approximately 12 patients treated at the MTD to more fully characterize the safety, tolerability, and PK of MLN4924 with docetaxel and to evaluate disease response.

1.4.3.3 Dose and Schedule for Treatment With Paclitaxel + Carboplatin (Plus MLN4924, Arm 2)

Carboplatin Dose and Schedule (Lead-in Cohort)

Before enrolling patients in Arm 2 with paclitaxel + carboplatin, 3 patients will be treated with carboplatin AUC6 and MLN4924 at 15 mg/m^2. The absence of a DLT in this lead-in cohort during Cycle 1 will trigger enrollment in the dose escalation phase of Arm 2. In the event that 1 DLT is observed in this lead-in, an additional 3 patients may be treated with the same combination. Observing no more than 1 DLT in this lead-in cohort will trigger enrollment on Arm 2 at AUC6 (MLN4924 [15 mg/m^2] + paclitaxel [200 mg/m^2] + carboplatin [AUC6]).

If a total of 2 or more DLTs are observed in this lead-in cohort, enrollment on Arm 2 will open at reduced doses of carboplatin (AUC5) and paclitaxel (175 mg/m^2), and the patients will receive MLN4924 (15 mg/m^2) + paclitaxel (175 mg/m^2) + carboplatin (AUC5).

Paclitaxel + Carboplatin Dose and Schedule (Dose Escalation Phase)

In the dose escalation phase, paclitaxel will be administered by IV infusion at a dose of 200 mg/m^2 (or 175 mg/m^2 if the dose is modified in the lead-in phase), in combination with carboplatin (AUC6 or AUC5 depending on results of the carboplatin lead-in cohort) and MLN4924 doses. Once the MTD of MLN4924 + paclitaxel + carboplatin is reached, approximately 6 additional patients will be enrolled for a total of approximately 12 patients treated at the MTD to more fully characterize the safety, tolerability, and PK of MLN4924 with paclitaxel + carboplatin and to evaluate disease response.

1.4.3.4 Dose and Schedule for Treatment With Gemcitabine (Plus MLN4924, Arm 3)

In the dose escalation phase, gemcitabine will be administered by IV infusion at a dose of 1000 mg/m^2 in combination with MLN4924 doses. The planned doses of MLN4924 are 25, 50, 75, and 100 mg/m^2. Once the MTD of MLN4924 + gemcitabine is reached, approximately 6 additional patients will be enrolled for a total of approximately 12 patients treated at the MTD to more fully characterize the safety and tolerability of MLN4924 with gemcitabine and to evaluate disease response.

Gemcitabine is initially dosed at 1000 mg/m^2 in Arm 3. If it is determined by the sponsor that 1000 mg/m^2 is poorly tolerated by multiple patients, then the initial dose for all patients subsequently enrolled in that arm may be reduced to a gemcitabine dose of 800 mg/m^2. For

patients who start on a gemcitabine dose of 800 mg/m^2, dose modification would be allowed by 1 level to 600 mg/m^2. No further dose modification below 600 mg/m^2 is allowed.

1.4.4 Rationale for Assessment of Biomarkers of Response

CCI

[redacted]

1.5 Potential Risks and Benefits

Given limited existing clinical experience, it is not known whether tumors will respond to treatment with MLN4924. However, a number of patients treated with MLN4924 did demonstrate clinical benefit based primarily on prolonged SD (see Section 1.3). In addition, it is anticipated that the SoC therapies used in this study may provide additional clinical benefit to patients.

1.5.1 Risks of MLN4924 Therapy

Safety information gained from single-agent clinical studies of MLN4924 and from toxicology studies in rats and dogs has been used to guide the safety evaluation of MLN4924. Additional information on risks is provided in the IB and the Development Core Safety Information (DCSI) to the IB.

Based on preliminary findings from the single-agent clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, the risks of MLN4924 treatment are presented below.

Identified Risks

- Increased heart rate
- Diarrhea
- Nausea
- Vomiting
- Pyrexia
- Liver function test (LFT) abnormal
- Musculoskeletal pain
- Myalgia

Potential Risks

There are potential risks in the MLN4924 program that require further monitoring. While the potential toxicities listed below may be severe or life-threatening, it is anticipated that they can be managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities for at least 30 days after their last dose of MLN4924.

Potential Risks From Phase 1 Studies (at High Doses)

There are events that have been reported in phase 1 studies at doses and schedules substantially higher (≥110 mg/m^2) than those being used in current clinical studies of MLN4924. These events are considered potential risks for the doses and schedules proposed in this study.

- Multi-organ failure that could result in death.
- Renal failure.
  - The events of multi-organ failure (hepatic, renal, and cardiac) with a fatal outcome, and renal failure alone, have been reported at doses of MLN4924 ranging from 110 to 278 mg/m^2. Refer to the current IB for additional information about multi-organ failure and dosing.

- Cardiac arrhythmias.
  - All events were supraventricular arrhythmias; all except 1 were unrelated. The case of atrial fibrillation, assessed by the investigator as related, occurred in a patient with a risk factor for cardiovascular disease (uncontrolled hypertension).
- Gastrointestinal (GI) toxicity including or resulting in dehydration and electrolyte imbalance.
- Acute phase response.
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia.
- Hypophosphatemia.

Potential Risks Confounded by Underlying Disease or Malignancy

Events have been reported from clinical studies that are confounded by the patient's underlying medical condition, including malignancy. These events are noted in the absence of randomized, controlled data:

- Fatigue
- Chills
- Decreased appetite
- Neutropenia
- Febrile neutropenia
- GI bleeding
  - All events were assessed by the investigator as unrelated; the majority occurred in the setting of thrombocytopenia.

Potential Risks Primarily Based on Findings From Animal Studies

Potential risks that are derived from findings in animal studies in rats and dogs include the following:

- Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure (BP), and increased diastolic BP.
- Enteropathy (including dehydration and electrolyte loss) with secondary sepsis.

- Effects on the testes and ovaries that represent a reproductive hazard, including sterility.
- Increased developmental risk to the fetus or embryo.
- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Local tissue injury when administered SC.
- Prolongation of the activated partial thromboplastin time (aPTT).
- Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high), but not in dogs. This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.

It is possible that MLN4924 will have toxicities, which may be severe or fatal, that were not observed in or predicted from the studies completed in rats and dogs or have not yet been identified in patients.

Hepatotoxicity has been noted following administration of MLN4924 in patients with advanced malignancy, including elevations of liver transaminases, alkaline phosphatase (ALP), and bilirubin. Liver enzymes and liver function are frequently monitored during clinical studies of MLN4924. Agents such as acetaminophen and acetaminophen-containing products should not be administered to patients 24 hours before, the day of, and 24 hours after dosing with MLN4924 (see Section 6.6).

Patients must be carefully evaluated at screening and before each MLN4924 dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Guidance on rehydration is provided in Section 6.9.

These potential toxicities will be managed by careful, frequent monitoring and intervention, as needed, with supportive care. It is possible that MLN4924 will have toxicities that were not observed in, or predicted from, the studies completed in rats and dogs or have not yet been identified in patients.

Patients will be monitored closely for these anticipated and potential toxicities and for unanticipated toxicities when they are receiving this agent and for at least 30 days after their

last dose. Monitoring will include the following: laboratory assessments, physical examinations, SAE and AE reporting, and safety review before each dose escalation (see Section 9.1). Although therapeutic efficacy is a desired outcome of treatment with the study drugs, it is unknown whether patients will benefit from this study. In this dose escalation study, the dose will be escalated by cohort.

To limit the risks to patients, the first patient enrolled at each dose level of MLN4924 with SoC, as applicable, will be observed for 7 days before the remaining 2 patients of the cohort are treated. These 3 patients will be observed through completion of the first cycle, before additional patients are treated at the next dose level. The requirement for this 1-week wait period may be removed in subsequent cohorts if it is judged by the sponsor that combination therapy administered in a given arm may be administered without a major safety concern.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International Council for Harmonisation [ICH] guidelines).

1.5.2 Risks of Docetaxel Treatment

Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

Severe hypersensitivity, including very rare, fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of docetaxel and administration of appropriate therapy.

Docetaxel is contraindicated if the patient has a history of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80.

Severe fluid retention may occur despite dexamethasone.

For more details, refer to the Taxotere® (docetaxel) United States (US) Package Insert.[16]

1.5.2.1 Hepatotoxicity Warning

Docetaxel should not be given if total bilirubin is greater than the upper limit of the normal range (ULN), or if aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) are greater than 1.5 times the ULN. LFT elevations increase the risk of severe or life-threatening complications. LFTs should be obtained before each treatment cycle.

1.5.2.2 Hematologic Warning

Docetaxel should not be given if the absolute neutrophil count (ANC) is less than 1500 cells/mm^3.

1.5.2.3 Risks of MLN4924 and Docetaxel as Combination Therapy

Based on the known individual safety profiles of MLN4924 and docetaxel, the following potential risks of combination therapy may apply: death, hypersensitivity, hepatoxicity, neutropenia, and fluid retention (cardiac/pulmonary). With regard to docetaxel, treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

1.5.3 Risks of Carboplatin and Paclitaxel Therapy

See Section 15.1 for information on the hematologic toxicity of carboplatin alone and in combination with paclitaxel.

1.5.3.1 Carboplatin

Anaphylaxis-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Vomiting is another frequent drug-related side effect.

Carboplatin Injection is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds.

Carboplatin Injection should not be employed in patients with severe bone marrow depression or significant bleeding.

For more details, please refer to the Paraplatin® (carboplatin) US Package Insert.[17]

Nephrotoxicity Warning

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

Hematologic Warning

Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved.

Anemia may be cumulative and may require transfusion support.

1.5.3.2 Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Severe conduction abnormalities have been documented in less than 1% of patients during paclitaxel therapy and, in some cases, require pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

For more details, please refer to the Taxol® (paclitaxel) US Package Insert.[18]

Hematologic Warning

Paclitaxel Injection, USP therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3. To monitor for the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Paclitaxel Injection, USP.

1.5.3.3 Risks of MLN4924 and Paclitaxel + Carboplatin as Combination Therapy

Based on the known individual safety profiles of MLN4924 and paclitaxel + carboplatin, the following potential risks of combination therapy may apply: bone marrow suppression,

hypersensitivity/anaphylaxis reactions, and hepatotoxicity. Renal effects of nephrotoxic compounds (see Section 15.8) may be potentiated by carboplatin.

1.5.4 Risks of Gemcitabine Therapy

The most common adverse reactions for the single agent (≥ 20%) are nausea and vomiting, anemia, elevated liver enzymes (ALT and AST), neutropenia, leukopenia, ALP, proteinuria, fever, hematuria, rash, thrombocytopenia, and dyspnea.

Gemcitabine is contraindicated in patients with a known hypersensitivity to gemcitabine.

For more details, please refer to the Gemzar® (gemcitabine) US Package Insert.[19]

1.5.4.1 Hematologic Warning

Myelosuppression can be a DLT; blood counts should be monitored.

1.5.4.2 Renal Warning

Renal function should be monitored before initiation of therapy and periodically thereafter. Gemcitabine should be used with caution in patients with renal impairment. Cases of hemolytic uremic syndrome (HUS) and/or renal failure, some fatal, have occurred. Discontinue gemcitabine for HUS or severe renal toxicity.

1.5.4.3 Hepatic Warning

Hepatic function should be monitored before initiation of therapy and periodically thereafter. Gemcitabine should be used with caution in patients with hepatic impairment. Serious hepatotoxicity, including liver failure and death, has occurred. Discontinue gemcitabine for severe hepatic toxicity.

1.5.4.4 Risks of MLN4924 and Gemcitabine as Combination Therapy

Based on the known individual safety profiles of MLN4924 and gemcitabine, the following potential risks of combination therapy may apply: myelosuppression, renal toxicity, and hepatotoxicity.

1.5.4.5 Summary of Risks of Standard of Care Therapies in Combination With MLN4924

Potential overlapping toxicities of SoCs in combination with MLN4924 that are described in more detail above are summarized in Table 1-1.

Table 1-1 Potential Overlapping Toxicities With MLN4924

Standard of Care	Potential Overlapping Toxicities With MLN4924
Docetaxel	Death[a]
	Hypersensitivity
	Hepatoxicity
	Neutropenia
	Fluid retention (cardiac/pulmonary)
Paclitaxel/Carboplatin	Bone marrow suppression
	Hypersensitivity/anaphylaxis reactions
	Hepatotoxicity
	Renal effects of nephrotoxic compounds may be potentiated by carboplatin
Gemcitabine	Renal toxicity
	Hepatic toxicity
	Myelosuppression

a Docetaxel treatment-related mortality increases with abnormal liver function, occurs at higher doses, and in patients with non-small cell lung cancer who received prior platinum-based therapy and are receiving docetaxel at 100 mg/m^2.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are:

- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with docetaxel in patients with solid tumors
- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with paclitaxel and carboplatin in patients with solid tumors
- To establish the MTD and assess the safety and tolerability of MLN4924 in combination with gemcitabine in patients with solid tumors

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate disease response that may be observed with the combination of MLN4924 and docetaxel

- To evaluate disease response that may be observed with the combination of MLN4924, paclitaxel, and carboplatin

- To evaluate disease response that may be observed with the combination of MLN4924 and gemcitabine

- To measure plasma MLN4924 concentrations to contribute to a population PK analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine in patients with solid tumors

2.3 Exploratory Objectives

The exploratory objectives include:

CCI [redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints include AEs, SAEs, assessments of clinical laboratory values and clinically important laboratory abnormalities, and vital sign measurements.

3.2 Secondary Endpoints

The secondary endpoints include:

- Measures of disease response including objective response rate and duration of response based on investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1)

- MLN4924 plasma concentration–time data for population PK analysis

3.3 Exploratory Endpoints

CCI [redacted]

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label, multicenter, phase 1b, dose escalation study of MLN4924 in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine in adult patients with solid tumors (patients in the carboplatin lead-in cohort will receive MLN4924 + carboplatin only). The patient population will consist of patients 18 years of age or older with nonhematologic malignancies who, according to the investigator's medical judgment, could potentially benefit from treatment with any of the 3 SoC therapies being studied.

It is expected that approximately 69 patients will be enrolled in this study. During the dose escalation portion of this study, the following dose levels of IV MLN4924 are planned to be studied in combination with docetaxel (Arm 1), paclitaxel + carboplatin (Arm 2), or gemcitabine (Arm 3).

MLN4924 + Docetaxel (Arm 1): A total of 4 dose levels of IV MLN4924 (15, 25, 37, and 50 mg/m^2) are planned to be studied in combination with 75 mg/m^2 of docetaxel. On Day 1 of each cycle when both drugs are administered, docetaxel will be administered first at a dose of 75 mg/m^2 IV over 1 hour. After a mandatory approximately 15-minute time out (MLN4924-free period), MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days. No dose reduction of MLN4924 below 15 mg/m^2 is allowed.

MLN4924 + Carboplatin Lead-in Cohort (before Arm 2): Before patients are enrolled in Arm 2 with paclitaxel + carboplatin, a cohort of approximately 3 to 6 patients will be treated with AUC6 dose of carboplatin in combination with MLN4924 at a dose of 15 mg/m^2. On Day 1 of each cycle, both compounds will be given. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days. If 1 DLT is seen in this cohort, 3 additional patients will be treated with the same combination regimen. The carboplatin dose may be reduced to AUC5 for safety as needed (see Section 6.5 for further details). No dose reduction of MLN4924 below 15 mg/m^2 is allowed. No dose escalation of MLN4924 is planned in this cohort. The only chemotherapy agent that patients in this lead-in cohort will

receive is carboplatin; these patients will not enroll on the MLN4924 + paclitaxel + carboplatin phase (Arm 2).

Observing no more than 1 DLT in this lead-in cohort will trigger enrollment in Arm 2 at AUC6 (MLN4924 [15 mg/m^2] + paclitaxel [200 mg/m^2] + carboplatin [AUC6]), and patients will be treated as described below for Arm 2.

If a total of 2 or more DLTs are observed in this cohort, enrollment in Arm 2 will open at reduced paclitaxel and carboplatin doses (MLN4924 [15 mg/m^2] + paclitaxel [175 mg/m^2] + carboplatin [AUC5]), and patients will be treated as described below for Arm 2.

MLN4924 + Paclitaxel + Carboplatin (Arm 2): During the dose escalation phase, a total of 4 dose levels of IV MLN4924 (15, 25, 37, and 50 mg/m^2) are planned to be studied in combination with paclitaxel and carboplatin. On Day 1 of each cycle when all 3 drugs are administered, paclitaxel is given first at a dose of 200 mg/m^2 (or 175 mg/m^2, if the dose was reduced in the carboplatin lead-in cohort) IV over 3 hours followed by carboplatin AUC6 (or AUC5 if the dose was reduced in carboplatin lead-in cohort) over 30 minutes. After a mandatory approximately 15-minute time out (MLN4924-free period) after carboplatin administration, MLN4924 will be administered IV. On Days 3 and 5, only MLN4924 will be given. The duration of each cycle will be 21 days.

MLN4924 + Gemcitabine (Arm 3): A total of 4 dose levels of IV MLN4924 (25, 50, 75, and 100 mg/m^2) are planned to be studied in combination with 1000 mg/m^2 of gemcitabine. Gemcitabine will be administered IV at a dose of 1000 mg/m^2 over 30 to 60 minutes or per current prescribing guidelines. After a 15-minute time out, MLN4924 will be administered. Patients will receive both agents on Days 1, 8, and 15, and the duration of each cycle will be 28 days.

After the determination of the MTD of MLN4924 with docetaxel (Arm 1), paclitaxel + carboplatin (Arm 2), and gemcitabine (Arm 3), approximately 6 additional patients will be enrolled to each arm for a total of approximately 12 patients treated in each arm at the MTD to more fully characterize the safety, tolerability, and PK of MLN4924 in combination with each SoC regimen and to evaluate disease response.

An adaptive approach using a CRM will be used for dose escalation (see Section 6.4). The CRM models the relationship between toxicities and dose level, which yields accurate and precise estimates of the MTD.[10, 20, 21] The dose toxicity relationship and the PMTD level will be updated as new data become available. The recommendation to escalate, de-escalate,

or expand at the same dose level will be determined by comparing the PMTD level from the dose toxicity model to the prespecified dose levels. From the starting dose, subsequent increases will be made according to the dose levels indicated for each arm; however, for safety reasons, no dose level will be skipped, and a minimum of 3 patients is required before escalating to the next dose level. Once at least 6 patients are treated at any dose level and the algorithm does not recommend escalation or de-escalation, this dose level may be considered the MTD.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010.[(1)] DLTs are defined in Section 6.3.

Throughout the study, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained and assessed to evaluate the safety and tolerability of MLN4924 in combination with docetaxel, paclitaxel + carboplatin, and gemcitabine (patients in the carboplatin lead-in cohort will receive MLN4924 + carboplatin only).

Blood samples (sparse sampling) for the determination of MLN4924 plasma concentrations and, if appropriate, its metabolites will be collected from each patient during Cycle 1 of treatment to contribute to a population PK analysis of MLN4924 co-administered with docetaxel, or paclitaxel + carboplatin, or gemcitabine. During the dose escalation portion of the study (excluding the Arm 2 carboplatin lead-in cohort), blood samples will be collected from each patient for the determination of MLN4924 plasma concentrations during the first cycle of treatment at the time points indicated in the Schedules of Events. During the MTD expansion portion of the study, serial blood samples will be collected from all patients at the time points indicated in the Schedules of Events before and after the start of MLN4924 infusion.

Computed tomography (CT) scans with IV contrast of the chest, abdomen, and pelvis will be performed during screening. CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter (Cycles 4-12) or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 1), and at the End of Study (EOS) visit. Additional CT scans may be performed, per investigator's discretion, if clinically indicated. If CT scan does not provide adequate imaging, magnetic resonance

imaging (MRI) may be used to evaluate sites of disease. Tumor response will be assessed by the investigator at these times using the RECIST, version 1.1.[22]

After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (extended up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment (Section 6.5) upon return from a treatment break, before treatment.

Paraffin-embedded tumor tissue or unstained slides of the tumor tissue will be collected at screening to enable genetic characterization of the patient's tumor [redacted]

4.2 Number of Patients

Approximately 69 total patients (approximately 6 patients in the MLN4924 + carboplatin lead-in cohort, approximately 15 patients in each arm of the dose escalation phase, and approximately 6 additional patients in each arm of the MTD dose expansion phase) will be enrolled in this study in approximately 10 study centers in the US. The definition of enrollment is provided in Section 7.4.13.

For determination of the MTD in the dose escalation phase, patients will be replaced if withdrawn from treatment during Cycle 1 for reasons other than DLT.

4.3 Duration of Study

Patients are treated for up to 12 cycles or until they experience symptomatic deterioration or progressive disease (PD) (see definition in Section 15.2), until their treatment is discontinued for another reason (see Section 7.6), or until the study is stopped. The maximum duration of treatment will be 12 cycles; however, if it is determined after discussion between by the investigator and the sponsor that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy or receive MLN4924 as a single agent beyond 12 cycles. After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (extended up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment (Section 6.5) upon return

from a treatment break, before treatment. The final analyses for the clinical study report will be conducted after all patients enrolled in the study have had the opportunity to complete at least 4 cycles of treatment with MLN4924 in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine.

The duration of enrollment, inclusive of dose escalation and MTD expansion, will be approximately 13 months.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years of age or older.
2. ECOG PS 0 or 1 (refer to Section 15.3).
3. Patients must have a histologically or cytologically confirmed metastatic or locally advanced and incurable solid tumor that is felt to be appropriate for treatment with 1 of the 3 chemotherapy regimens in this study, or have progressed despite standard therapy, or for whom conventional therapy is not considered effective. The tumor must be radiographically or clinically evaluable and/or measurable.
4. Recovered (ie, ≤ Grade 1 toxicity) from the effects of prior antineoplastic therapy.
5. Suitable venous access for the study-required blood sampling for MLN4924 PK assessments.
6. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
7. Clinical laboratory values as specified below within 3 days before the first dose of study drug:
   - ANC ≥ 1,500/mm^3 (refer to Section 15.4)
   - Platelet count ≥ 100,000/mm^3
   - Total bilirubin ≤ the ULN

- Prothrombin time (PT) and aPTT ≤ 1.5 × ULN
- ALT, AST, and ALP ≤ 2.5 × ULN
    - For patients to be enrolled in Arm 1 (MLN4924 + docetaxel) only: AST/ALT must be ≤ 1.5 × ULN, and total bilirubin should be within the normal range.
- Serum creatinine ≤ 1.2 mg/dL or calculated/measured creatinine clearance ≥ 50 mL/minute (see Section 15.5)

8. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - As of Amendment 1, if they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Section 15.9), at the same time, from the time of signing the informed consent form (ICF) through 4 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only ([as of Amendment 1], and lactational amenorrhea [as of Amendment 1] are not acceptable methods of contraception. Female and male condoms should not be used together.)

    Male patients, even if surgically sterilized (ie, status postvasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only [as of Amendment 1], and lactational amenorrhea [as of Amendment 1] are not

acceptable methods of contraception. Female and male condoms should not be used together.)

9. Patients who are willing to refrain from donating blood for at least 90 days after their final dose of MLN4924 and (for male patients) willing to refrain from donating semen for at least 4 months after their final dose of MLN4924.

10. Availability of fixed tumor specimen (block or slides) for exploratory biomarker analysis. If no slides or block are available, fresh tumor biopsies should be obtained and used for these assessments.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.
2. Major surgery within 14 days before the first dose of study treatment.
3. Active uncontrolled infection or severe infectious disease, such as pneumonia, meningitis, septicemia, or methicillin-resistant Staphylococcus aureus infection.
4. Receiving antibiotic therapy within 14 days before the first dose of study treatment.
5. Life-threatening illness unrelated to cancer.
6. Known hypersensitivity to study-assigned chemotherapy.
7. Prior treatment with MLN4924; however, prior treatment with docetaxel, paclitaxel, carboplatin, and gemcitabine is allowed.
8. History of severe hypersensitivity reactions to docetaxel (polysorbate 80-based formulations) for patients to be enrolled in Arm 1 (MLN4924 + docetaxel), history of hypersensitivity to carboplatin for patients to be enrolled in carboplatin lead-in cohort or Arm 2 (MLN4924 + paclitaxel + carboplatin), or history of severe hypersensitivity to paclitaxel (cremophor-based formulations) for patients to be enrolled in Arm 2.
9. Persistent diarrhea (≥ Grade 2) lasting > 3 days within 2 weeks before the first dose of study treatment.

10. Systemic antineoplastic therapy within 21 days preceding the first dose of study treatment.
11. Radiotherapy within 14 days preceding the first dose of study treatment.
12. Prior treatment with radiation therapy involving ≥ 25% of the hematopoietically active bone marrow.
13. Treatment with CYP3A inducers within 14 days before the first dose of MLN4924. Treatment with CYP3A inhibitors within 14 days before the first dose of MLN4924; however, voriconazole and fluconazole need only be stopped for 3 days before MLN4924 (see Section 6.7 for criteria for restarting these azole antifungals). Moderate and strong CYP3A inhibitors and CYP3A inducers were not permitted. Following implementation of Amendment 1 and completion of at least 12 cycles of treatment, concomitant use of moderate and strong CYP3A inhibitors is permitted in Arm 2 (study arm with active patients) (see Table 6-4 and Section 15.7). Patients must have no history of amiodarone use in the 6 months before the first dose of MLN4924.
14. Clinically significant central nervous system (CNS) disease defined as untreated, progressive, or requiring steroids for control of symptoms.
15. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
16. Treatment with any investigational products within 21 days preceding the first dose of study treatment.
17. Patients currently taking statins who are unwilling or unable to refrain from using statins 24 hours before, the day of, and 24 hours after each MLN4924 administration.
18. Known human immunodeficiency virus (HIV) positive or hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.

    Note: Patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.

19. Known hepatic cirrhosis.

20. Known cardiac/cardiopulmonary disease, defined as 1 of the following:

    - Uncontrolled high blood pressure (ie, systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg)
    - Congestive heart failure New York Heart Association (NYHA) Class III or IV, or Class II with a recent decompensation requiring hospitalization within 4 weeks before screening (Section 15.6)
    - Unstable angina, myocardial infarction, or angioplasty procedure with coronary artery stent placement within 12 months before screening
    - Arrhythmia (history of polymorphic ventricular fibrillation; torsade de pointes; permanent atrial fibrillation [a fib], defined as continuous a fib for ≥ 6 months; and persistent a fib, defined as sustained a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening. Patients with paroxysmal a fib are permitted to enroll, provided that they are rate controlled on a stable regimen.)
    - Implantable cardioverter defibrillator
    - Grade 3 or greater valvular disease
    - Grade 3 or greater pulmonary hypertension
    - Prolonged rate corrected QT (QTc) interval ≥ 500 msec, calculated according to institutional guidelines

21. Left ventricular ejection fraction (LVEF) < 50% as assessed by echocardiogram or radionuclide angiography.
22. Patients with a cardiac pacer whose heart rate is set at a fixed rate and patients on concomitant medication that may limit increase in heart rate in response to hypotension (eg, high-dose beta blocker)
23. History of severe intolerance to cytotoxic agent(s) given in the assigned arm

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

See Table 6-1 for an overview of MLN4924 and SoC dosing. All doses must be taken as outlined in the Schedules of Events. However, Day 1 dosing may be delayed by up to 2 days (Cycles 1-12) or up to 2 weeks (after completion of Cycle 12; extended up to 4 weeks after consulting with the sponsor) to accommodate inclement weather, holidays, vacations, or other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment within this time, the patient may continue the study only with the written permission of the Millennium project clinician or designee. See Section 7.4 for information about corresponding study procedures if dosing is delayed for reasons as noted above. After completion of at least 12 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (extended up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment (Section 6.5) upon return from a treatment break, before treatment. Refer to the Study Manual for additional instructions regarding study drug administration.

Table 6-1 Overview of MLN4924 and Standard of Care Dosing

Arm	Cycle Duration (days)	Starting Dose[a] (mg/m^2)	Dosing Day				
			1	3	5	8	15
Arm 1							
MLN4924	21	15	X	X	X		
Docetaxel	21	75	X				
Arm 2 Carboplatin Lead-in Cohort							
MLN4924	21	15	X	X	X		
Carboplatin	21	AUC6	X				
Arm 2							
MLN4924	21	15	X	X	X		
Paclitaxel	21	200[b]	X				
Carboplatin	21	AUC6[b]	X				
Arm 3							
MLN4924	28	25	X			X	X
Gemcitabine	28	1000	X			X	X

Abbreviations: MTD=maximum tolerated dose.

a In the dose escalation phase, the MLN4924 dose will be increased until the MTD is reached. The following planned dose levels will be evaluated for Arm 1, Arm 2 carboplatin lead-in cohort, and Arm 2: 15, 25, 37, and 50 mg/m^2; and for Arm 3: 25, 50, 75, and 100 mg/m^2. The MTD of MLN4924 will be administered during the dose expansion phase.

b If the dose of carboplatin is reduced from AUC6 to AUC5 in the carboplatin lead-in cohort, enrollment in Arm 2 will open at a reduced dose of carboplatin and paclitaxel (MLN4924 [15 mg/m^2] + paclitaxel [175 mg/m^2] + carboplatin [AUC5]).

6.1.1 MLN4924 Administration

Patients will receive MLN4924 diluted with 5% dextrose in a 250-mL bag via a 1-hour (±10 minutes as of Amendment 1) IV infusion. MLN4924 should be administered through central or peripheral venous access. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours.

The entire content of the MLN4924 IV bag will be infused at a constant rate over 1 hour (±10 minutes as of Amendment 1). The start and end time of IV infusion should be recorded accurately. To ensure that all the MLN4924 is administered, the infusion line will be flushed with saline or 5% dextrose immediately after administration. The volume used for line flushing is not considered part of the volume of the MLN4924 IV bag to be documented.

6.1.2 Docetaxel Administration

Docetaxel will be administered as a 1-hour IV infusion at a dose of 75 mg/m^2 on Day 1 combined with escalating IV doses of MLN4924 on Days 1, 3, and 5. Refer to the most recent prescribing information for further details regarding docetaxel administration.

6.1.2.1 Premedication for Docetaxel-Associated Hypersensitivity or Other Acute Reactions Guidelines

Premedication to prevent docetaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with dexamethasone (Decadron, 4 mg BID for 3 days), which should start 24 hours before docetaxel administration.

6.1.3 Carboplatin Administration

Carboplatin will be administered as a 30-minute IV infusion at a dose of AUC6 on Day 1 combined with escalating IV doses of MLN4924 on Days 1, 3, and 5. Refer to the most recent prescribing information for further details regarding carboplatin administration.

> *If a patient's glomerular filtration rate (GFR) is estimated based on serum creatinine measurements by the standardized Isotope Dilution Mass Spectrometry method, FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as:*
>
> *Total Carboplatin Dose (mg)=(target AUC) × (GFR + 25) [Calvert formula]*
>
> *Maximum Carboplatin Dose (mg)=target AUC (mg × min/mL) × (150 mL/min)*
>
> *The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.*
>
> *For a target AUC=6, the maximum dose is 6 × 150=900 mg*
>
> *For a target AUC=5, the maximum dose is 5 × 150=750 mg*
>
> *For a target AUC=4, the maximum dose is 4 × 150=600 mg*

Source: fda.gov, "Carboplatin dosing," accessed 19 February 2013.

6.1.4 Paclitaxel Administration

Paclitaxel will be administered as a 3-hour IV infusion at a dose of 200 mg/m^2 on Day 1 combined with escalating IV doses of MLN4924 on Days 1, 3, and 5. Refer to the most recent prescribing information for further details regarding paclitaxel administration.

6.1.4.1 Premedication for Paclitaxel-Associated Hypersensitivity or Other Acute Reactions

Premedication to prevent paclitaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with either dexamethasone (10 mg) 24 hours before and on the day of paclitaxel dosing or methylprednisolone (solu-Medrol) immediately before paclitaxel dosing.

6.1.5 Gemcitabine Administration

Gemcitabine will be administered as a 30- to 60-minute IV infusion before MLN4924 on Days 1, 8, and 15 or per current prescribing guidelines. Refer to the most recent prescribing information for further details regarding gemcitabine administration.

Gemcitabine is initially dosed at 1000 mg/m^2 in Arm 3. If it is determined by the sponsor that 1000 mg/m^2 is poorly tolerated by multiple patients, then the initial dose for all patients subsequently enrolled in that arm may be reduced to a gemcitabine dose of 800 mg/m^2. For patients who start on a gemcitabine dose of 800 mg/m^2, dose modification would be allowed by 1 level to 600 mg/m^2. No further dose modification below 600 mg/m^2 is allowed.

6.2 Reference/Control Therapy

No reference or placebo treatment will be used in this study. All eligible patients will receive treatment with MLN4924 in combination with docetaxel, paclitaxel + carboplatin, or gemcitabine. Patients in the carboplatin lead-in cohort will receive MLN4924 + carboplatin only.

6.3 Definitions of Dose-Limiting Toxicity

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010.[(1)] These criteria are provided in the Study Manual. DLT will be defined as any of the following events that are considered by the investigator to be at least possibly

related to therapy with MLN4924, docetaxel, carboplatin, paclitaxel and carboplatin, or gemcitabine. When a dose modification is warranted for safety, and the toxicity is thought to be attributable to the chemotherapeutic agent(s), consider dose reductions for chemotherapy first, if appropriate. Dose modification of MLN4924 may also be considered for events judged by the investigator to be directly related to MLN4924 or chemotherapy-related toxicities that may have been exacerbated by MLN4924 in a combination setting.

Hematologic Dose-Limiting Toxicities

- Any Grade 4 hematologic toxicity using NCI CTCAE Version 4.03 with the exception of Grade 4 neutropenia lasting < 7 days in duration
- Grade 3 or greater neutropenia with fever > 38.5°C sustained for longer than 1 hour
- A delay in the initiation of Cycle 2 due to a lack of adequate recovery from treatment-related toxicity (recovery to Grade ≤ 1 or to the patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician) of 4 weeks or greater due to hematologic toxicity believed not related to tumor infiltration (bone marrow evaluation may be required)

Nonhematologic Dose-Limiting Toxicities

- Grade 3 or greater diarrhea that is uncontrolled despite maximal supportive therapy
- Grade 3 or greater nausea and/or emesis that is uncontrolled despite the use of optimal antiemetic prophylaxis. (Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-hydroxytryptamine 3 serotonin receptor antagonist and a corticosteroid given in standard doses and according to standard schedules.)
- Grade 3 or greater arthralgia/myalgia lasting longer than 48 hours that is uncontrolled despite the use of optimal analgesia
- Grade 3 or greater electrolyte disturbance that is uncontrolled despite appropriate medical management
- Any other Grade 3 or greater nonhematologic toxicity with the following exceptions:
    - Brief (< 1 week) fatigue

  - Hypophosphatemia that can be controlled with appropriate medical management

- A delay in the initiation of Cycle 2 of more than 2 weeks due to a lack of adequate recovery from non-hematologic toxicity (recovery to Grade ≤ 1 or to patient's baseline values, or to a level considered acceptable by the investigator after discussion with the project clinician)

- Other study drug-related, nonhematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy with MLN4924

Other Dose-Limiting Toxicities

In addition, the following will also be considered DLTs if they occur within the first cycle:

- Any AE at least possibly related to the study drugs, regardless of NCI CTCAE grade, leading to dose modification of MLN4924 or other study treatments (docetaxel, paclitaxel, carboplatin, or gemcitabine) in the next cycle.

- A patient who has received 2 of 3 gemcitabine doses (eg, Day 1 and Day 8, or Day 1 and Day 15) and has had a drug-related toxicity that does not qualify as a DLT per the guidelines above may continue with the next regularly scheduled cycle of treatment, and the missed dose will not constitute a DLT. However, if the patient receives only 1 gemcitabine dose per cycle due to a drug-related toxicity, then this toxicity will constitute a DLT.

Although AEs meeting the protocol-specified definition of DLT may occur at any point during treatment, only those AEs meeting the DLT definition occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

6.4 Dose Escalation Rules

An adaptive approach using a CRM will be used for dose escalation, as shown in Table 6-2. The starting dose for Arms 1 and 2 will be 15 mg/m^2, and the starting dose for Arm 3 will be 25 mg/m^2. The intervals between dose levels are prespecified and are not determined by the CRM algorithm. For Arms 1 and 2, the increases will be approximately 1.67-, 1.5-, and

1.33-fold over the previous dose level, and for Arm 3, the increases will be 2-, 1.5-, and 1.33-fold over the previous dose level (see Table 6-2).

Table 6-2 Planned MLN4924 Dose Levels

Arm 1 (MLN4924 + Docetaxel)		
Dose Level	**Approx. Dose Increase Factor**	**MLN4924 Dose (unit)**
1	(starting)	15 mg/m^2 (in combination with docetaxel)
2	1.67	25 mg/m^2 (in combination with docetaxel)
3	1.5	37 mg/m^2 (in combination with docetaxel)
4	1.33	50 mg/m^2 (in combination with docetaxel)
Arm 2 Carboplatin Lead-in (MLN4924 + Carboplatin)		
Dose Level	**Approx. Dose Increase Factor**	**MLN4924 Dose (unit)**
1	(starting)	15 mg/m^2 (in combination with carboplatin)
Arm 2 (MLN4924 + Paclitaxel + Carboplatin)		
Dose Level	**Approx. Dose Increase Factor**	**MLN4924 Dose (unit)**
1	(starting)	15 mg/m^2 (in combination with paclitaxel + carboplatin)
2	1.67	25 mg/m^2 (in combination with paclitaxel + carboplatin)
3	1.5	37 mg/m^2 (in combination with paclitaxel + carboplatin)
4	1.33	50 mg/m^2 (in combination with paclitaxel + carboplatin)
Arm 3 (MLN4924 + Gemcitabine)		
Dose Level	**Approx. Dose Increase Factor**	**MLN4924 Dose (unit)**
1	(starting)	25 mg/m^2 (in combination with gemcitabine)
2	2	50 mg/m^2 (in combination with gemcitabine)
3	1.5	75 mg/m^2 (in combination with gemcitabine)
4	1.33	100 mg/m^2 (in combination with gemcitabine)

Three patients will be dosed at the initial dose level. The PMTD from the CRM model will be updated based on the observed DLTs (as defined in Section 6.3) after patients have completed the first cycle of therapy. The following criteria will be used to determine the dose for the next patients (example values are provided for Arms 1 and 2; the same criteria will be used to determine the MTD for Arm 3):

1. If no DLTs are observed, the PMTD will be greater than the midpoint between 15 and 25 mg/m^2 (ie, 20 mg/m^2), and 3 patients will be dosed at 25 mg/m^2 (see below).

2. If 1 DLT is observed, the PMTD will be between 15 and 20 mg/m^2, and 3 additional patients will be dosed at 15 mg/m^2.

3. If 2 or more DLTs are observed, the arm will be stopped.

If 3 additional patients (a total of 6 patients) are dosed at the initial dose of 15 mg/m^2 (as described in Criterion 2 above), the decision to enroll additional patients or escalate to the next higher dose level will depend on the following criteria:

1. If a total of 1 DLT in the 6 patients is observed, the PMTD will be greater than 20 mg/m^2, and 3 patients will be dosed at 25 mg/m^2 (see below).

2. If a total of 3 or more DLTs in the 6 patients are observed, the arm will be stopped.

3. If a total of 2 DLTs in the 6 patients are observed, 2 additional patients (a total of 8 patients) will be dosed at 15 mg/m^2. If no DLTs are observed in the 2 additional patients, 15 mg/m^2 will be the MTD. If any DLTs are observed in the 2 additional patients, the arm will be stopped.

During treatment at the subsequent dose levels, dose escalation will depend upon the observed DLT rate in all previously treated patients.

A minimum of 3 patients at the current dose level is required before escalating to the next higher dose level, and no scheduled dose levels may be skipped. If a re-escalation occurs after a de-escalation, 3 patients will be treated at the next higher dose level. To decide whether to enroll additional patients to the current dose level, escalate to the next higher dose level, or de-escalate to the prior dose level, the midpoint between the current dose level and the next scheduled higher dose level (Mid_{high}) and the midpoint between the previous dose level and the current dose level (Mid_{low}) will be calculated. These assessments will be conducted by the sponsor, and the following rules will then be used:

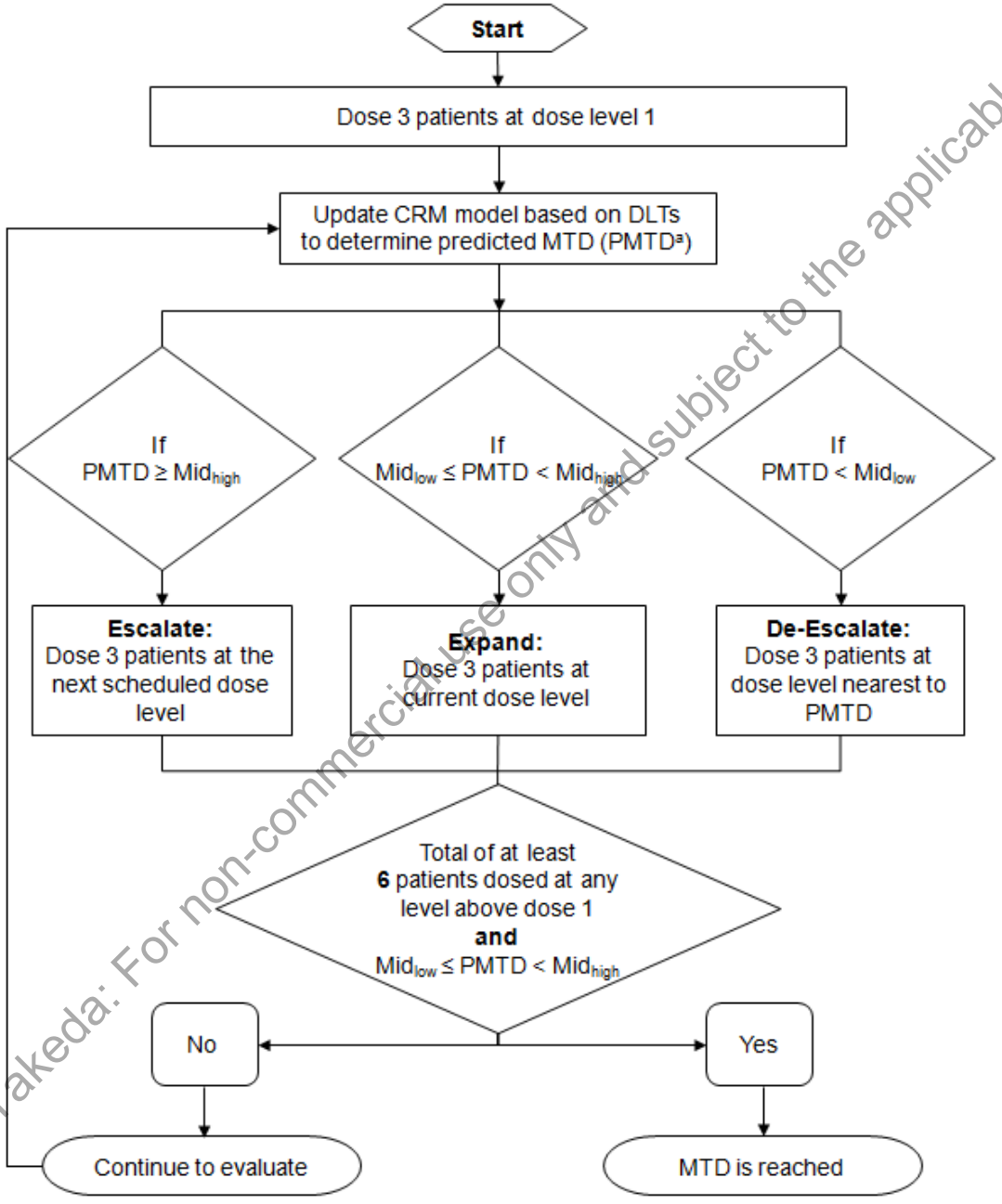
1. If the PMTD is greater than or equal to Mid_{high}, 3 patients will be treated at the next higher dose level.

2. If the PMTD is between Mid_{low} and Mid_{high}, 3 additional patients will be treated at the current dose level.

3. If the PMTD is less than Mid_{low}, 3 additional patients will be treated at the dose level that is nearest to the PMTD.

Once at least 6 patients are treated at any dose level and the algorithm does not recommend escalation or de-escalation, this dose level may be considered the MTD of MLN4924 in combination with the SoC. Figure 6-1 is a diagrammatical representation of these rules.

Figure 6-1 Dose Escalation Scheme



Abbreviations: CRM=continual reassessment method; DLT=dose-limiting toxicity; Mid_{high}=midpoint between current dose level and next dose level; Mid_{low}=midpoint between previous dose level and current dose level; MTD=maximum tolerated dose; PMTD=predicted MTD.

a The intervals between dose levels are prespecified and are not determined by the CRM algorithm.

After the determination of the MTD of MLN4924 with each SoC, approximately 6 additional patients will be enrolled to each arm, for a total of approximately 12 patients treated at the MTD, to more fully characterize the safety, tolerability, and PK of MLN4924 with SoC.

Although AEs meeting the protocol-specified definition of DLTs may occur at any point during treatment, only those AEs meeting the DLT definition occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels.

Patients who discontinue the study; experience dosing delay or dosing reduction in either MLN4924 or SoC, for reasons other than a DLT before they have completed all 21 days of Cycle 1 for Arms 1 and 2 or 28 days for Arm 3; or are administered MLN4924 in combination with SoC on unscheduled days in Cycle 1 will not be included in the assessment of the DLT rate at any given dose level. Such patients will be replaced. Patients who experience a DLT may be allowed to continue treatment with the study drugs at a dose level below that which was associated with the DLT.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible after discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity or exposure of MLN4924 in combination with SoC.

6.5 Dose-Modification Guidelines (Dose Delays, Dose Reductions, and Dose Interruptions)

The following apply to DLTs occurring during any cycle: for individual patients experiencing a DLT, treatment for each new cycle will be delayed until toxicity is reduced to ≤ Grade 1 or patient's baseline.

- Alopecia of any duration will not lead to dose modification or treatment delay.
- Patients can have a maximum of 2 dose modifications (if applicable) of chemotherapy agents and/or MLN4924 as outlined below. Patients who require more than 2 dose modifications will be discontinued from the study.
- Patients in the carboplatin lead-in cohort are initially dosed at AUC6. If ≥ 2 DLTs are seen in this cohort (see Section 1.4.3.3 for further details), further dosing with the carboplatin-containing regimen will be at AUC5.

- If the dose of carboplatin is reduced from AUC6 to AUC5 in the carboplatin lead-in cohort, enrollment on Arm 2 will open at a reduced dose of carboplatin and paclitaxel (MLN4924 [15 mg/m^2] + paclitaxel [175 mg/m^2] + carboplatin [AUC5]).

- Regardless of initial carboplatin dosing, patients in Arm 2 (MLN4924 + carboplatin + paclitaxel) may have their carboplatin dose reduced to no lower than AUC4. Patients who require further dose modifications will be discontinued from the study.

    - Paclitaxel is initially dosed at 200 mg/m^2. Up to 2 dose reductions to 175 mg/m^2 and 135 mg/m^2 may be considered.

    - Docetaxel is initially dosed at 75 mg/m^2. Up to 2 dose modifications to 60 mg/m^2 and 45 mg/m^2 may be considered.

    - Gemcitabine is initially dosed at 1000 mg/m^2. Up to 2 dose modifications to 800 mg/m^2 and 600 mg/m^2 may be considered.

    - MLN4924 is initially dosed at 15 mg/m^2 in Arms 1 and 2 or 25 mg/m^2 in Arm 3. Up to 2 dose modifications (to lower dose levels) may be considered. The lowest dose of MLN4924 cannot be lower than 15 mg/m^2 for Arms 1 and 2 or 25 mg/m^2 for Arm 3. Patients who require dose modifications below 15 mg/m^2 (in Arms 1 and 2) or below 25 mg/m^2 (in Arm 3) will be discontinued from the study.

- For the gemcitabine arm (Arm 3), the following dose modification will apply to the Day 8 and Day 15 dosing of each cycle:

    - Treat with full dose if the ANC is ≥ 1000 cells/μL and platelet count is ≥ 100,000 cells/μL.

    - Dose reduce gemcitabine to 800 mg/m^2 if the ANC is 500 to 999 cells/μL or the platelet count is 50,000 to 99,999 cells/μL.

    - Hold treatment if the ANC is < 500 cells/μL or platelet count is < 50,000 cells/μL.

- In the event of a DLT, hold treatment and provide supportive care until the patient recovers to Grade 1 toxicity or baseline level before considering a dose modifications as specified above. Patients with unresolved toxicities > Grade 1

lasting 3 weeks or longer from the date of the next scheduled treatment will not be permitted to continue on the study.

- When a dose modification is warranted for safety, consider dose reductions for chemotherapy first, if appropriate. Dose modification of MLN4924 may also be considered for events judged by the investigator to be directly related to MLN4924 or chemotherapy-related toxicities that may have been exacerbated by MLN4924 in a combination setting. For patients who take treatment breaks at the investigator's discretion, patient eligibility for continued treatment, including all Day 1 predose assessments specified in the Schedules of Events, will be confirmed by the investigator before resuming treatment. Treatment breaks must be no longer than 2 weeks in duration (extended up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively.

- The decision to treat at a reduced dose level of any therapy is at the discretion of the investigator. Discussions with the project clinician are encouraged.

Table 6-3 outlines the dose modification guidelines for specific toxicities.

Table 6-3 Dose Modification Guidelines for Specific Toxicities

NCI CTCAE Category	Severity	Action on Study Drug
Hematologic ANC	Febrile neutropenia	Hold dosing on Day 1 of Cycles ≥ 2 up to 3 weeks until febrile neutropenia is resolved, then resume dosing as appropriate. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	ANC < 1500 cells/µL on Day 1 of Cycles ≥ 2	Initiation (Day 1) of Cycles ≥ 2 should be delayed for up to 3 weeks until the ANC is ≥ 1500 cells/µL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	Grade ≥ 3 neutropenia lasting more than 7 days	Initiation (Day 1) of Cycles ≥ 2 should be delayed until the ANC is ≥ 1500 cells/µL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
Hematologic Platelets	Platelet count < 100,000/µL on Day 1 of Cycles ≥ 2	Initiation (Day 1) of Cycles ≥ 2 should be delayed for up to 3 weeks until the platelet count is ≥ 100,000 cells/µL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.

Table 6-3 Dose Modification Guidelines for Specific Toxicities

NCI CTCAE Category	Severity	Action on Study Drug
	Grade 4 thrombocytopenia lasting more than 7 days or the platelet count is < 25,000 cells/μL at any time	Initiation (Day 1) of Cycles ≥ 2 should be delayed until the platelet count is ≥ 100,000 cells/μL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.
Hematologic Modification applies only to the Day 8 and Day 15 dosing of gemcitabine	Gemcitabine arm (Arm 3) only:	Days 8 and 15 of each cycle: • Treat with full dose if the ANC is ≥ 1000 cells/μL and the platelet count is ≥ 100,000 cells/μL. • If the ANC is 500 to 999 cells/μL or platelet count is 50,000 to 99,999 cells/μL, dose reduce gemcitabine 1 dose level below that of the Day 1 dose of the current cycle (eg, if the Day 1 dose of the current cycle is 1000 mg/m^2, dose reduce to 800 mg/m^2; if the Day 1 dose of the current cycle is 800 mg/m^2, dose reduce to 600 mg/m^2). • Hold treatment if the ANC is < 500 cells/μL or the platelet count is < 50,000 cells/μL. For patients who had a dose withheld on Day 8 or Day 15, gemcitabine may be dose reduced by 1 dose level on subsequent cycles.
Hematologic Anemia	≥ Grade 1	No dose modification is allowed for anemia. Transfusion and/or erythropoietin may be given as clinically indicated for the treatment of anemia (see Section 6.9).
Nausea, emesis, or diarrhea despite maximal prophylaxis	≥ Grade 3	On days that both chemotherapy and MLN4924 are administered, hold all dosing for up to 3 weeks or until the toxicity returns to ≤ Grade 1, and restart at the next lower dose. On days when MLN4924 is given as a single agent, hold dosing of MLN4924 for up to 3 weeks or until the toxicity returns to ≤ Grade 1 before dosing is resumed. If treatment is delayed by more than 3 weeks, all treatments must be discontinued, and the patient comes off of the study. NOTE: Please ensure that optimal prophylaxis has been employed before dose reduction. Supportive care with CYP3A4 inducers should be avoided.
Stomatitis	≥ Grade 3	Hold treatment for up to 3 weeks until the stomatitis is ≤ Grade 1. If the stomatitis is not ≤ Grade 1 in 3 weeks, discontinue treatment. If acute ≥ Grade 3 stomatitis occurs at any time, the dose of chemotherapy should be reduced one level. This is a permanent dose reduction.

Table 6-3 Dose Modification Guidelines for Specific Toxicities

NCI CTCAE Category	Severity	Action on Study Drug
Hepatic toxicity	ALT/AST ≥ Grade 3 at any time	• If ALT or AST ≥ Grade 3 at any time, even during off-dosing days, then dose reduce MLN4924 by 1 dose level on subsequent dosing days. • This dose reduction is permanent. LFTs must have recovered to ≤ Grade 1 before each subsequent dosing. • In addition, if toxicity is felt to be attributable to the chemotherapy agent(s), then consider dose reduction for chemotherapy also by 1 dose level.
Hepatic toxicity	Total bilirubin >1.5 × ULN, regardless of AST/AST	Hold all dosing for up to 3 weeks until bilirubin returns to within normal range and/or dose reduce chemotherapy and/or MLN4924 by 1 level.
Cardiac toxicity	Symptomatic arrhythmia during infusion	Stop infusion, manage arrhythmia according to institutional guideline. Report as AE and discontinue further dosing.
Cardiac toxicity	Chest pain and/or symptomatic hypotension (< 90/60/mmHg)	Stop infusion. Perform an ECG. Give intravenous diphenhydramine and dexamethasone if hypersensitivity is thought to be the etiology. Also, consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. If > Grade 3, the patient comes off of the study.
Neurotoxicity (paclitaxel or docetaxel only)	≥ Grade 2	Hold treatment until patient recovers to Grade 1 toxicity then resume treatment at the next lower dose level. This will be a permanent dose reduction. Carboplatin, gemcitabine, or MLN4924 are not to be dose modified.
Allergic reaction (paclitaxel or docetaxel only	Moderate symptoms	Stop infusion. Give intravenous diphenhydramine 25 to 50 mg and intravenous dexamethasone 10 mg and/or treatment as per institutional guidelines. Resume infusion after recovery of symptoms at a low infusion rate. If no further symptoms, resume full dose rate until infusion is complete. If symptoms recur, stop infusion and discontinue patient.
Allergic reaction (paclitaxel or docetaxel only)	Severe symptoms	Stop infusion. Give intravenous diphenhydramine and dexamethasone and/or treatment as per institutional guidelines as above. Add epinephrine or bronchodilators if indicated. Report as an adverse event and discontinue patient.

Abbreviations: AE=adverse event; ANC=absolute neutrophil count; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ANC=absolute neutrophil count; CYP=cytochrome P450; ECG=electrocardiogram; LFTs=liver function tests; ULN=upper limit of normal.

6.5.1 Intrapatient Dose Escalation

No intrapatient dose escalation is allowed in this study.

6.6 Excluded Concomitant Medications and Procedures

Medications and procedures that are prohibited are listed in Table 6-4.

Table 6-4 Excluded Concomitant Medications and Procedures

Therapy	Comment
Acetaminophen and acetaminophen-containing products	Excluded only 24 hours before dosing, day of dosing, and 24 hours after dosing with MLN4924
Amiodarone	Excluded within 6 months before the first dose of MLN4924 and during the study
Azole antifungal agents	Generally excluded during the study but voriconazole and fluconazole may be used as specified in Section 6.7
Any investigational agent other than MLN4924	Excluded during the study
Known BCRP inhibitors (ie, cyclosporine and eltrombopag [Promacta])	Generally excluded during the study but may be used as specified in Section 6.7
Clinically significant CYP3A4 inducers (Section 15.7)	Excluded within 14 days before dosing with MLN4924 and during the study

Abbreviations: BCRP=breast cancer-resistance protein; CYP=cytochrome P450; P-gp=P-glycoprotein.

6.7 Permitted Concomitant Medications and Procedures

Medications and procedures that are specifically permitted during the study are listed in Table 6-5.

Table 6-5 Permitted Concomitant Medications and Procedures

Therapy	Comment
Azole antifungal agents	Permitted only if the patient's clinical condition requires the use of an azole antifungal agent. The patient may receive voriconazole and fluconazole from 24 hours after the last MLN4924 dose to 72 hours before the next MLN4924 dose. For example, if a patient receives MLN4924 on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then an azole may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Known BCRP substrates (ie, methotrexate and sulfasalazine) and known BCRP inhibitors (ie, cyclosporine and eltrombopag [Promacta])	Permitted only if the patient's clinical condition requires the use of a known BCRP substrate/inhibitor. The patient may receive it from 24 hours after the last MLN4924 dose to 72 hours before the next MLN4924 dose. For example, if a patient receives MLN4924 on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP substrate/inhibitor may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.

Table 6-5 Permitted Concomitant Medications and Procedures

Therapy	Comment
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Whenever possible, caution should be used with nephrotoxic concomitant medications (Section 15.8). Alternative concomitant non-nephrotoxic medications should be used whenever possible.
Known P-gp inhibitors (ie, **azithromycin [Zithromax],** captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor).	Permitted only if the patient's clinical condition requires the use of a known P-gp inhibitor. The patient may receive it from 24 hours after the last MLN4924 dose to 72 hours before the next MLN4924 dose. For example, if a patient receives MLN4924 on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the P-gp inhibitor may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Red blood cell transfusion	For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL during the conduct of the study, consideration should be given for red blood cell transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Red blood cell transfusions must be administered before administration of study drug (ie, at least 1 day before dosing). Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

Abbreviation: BCRP=breast cancer-resistance protein; P-gp=P-glycoprotein.

6.8 Precautions and Restrictions

Concomitant medications and procedures that are excluded or must be used with caution are described in Section 6.6 and Section 6.7, respectively.

Certain situations may warrant further caution, such as modifying the dose of study drug(s). Dose modification guidelines are provided in Section 6.5.

6.8.1 MLN4924

It is not known what effects MLN4924 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below and in Section 15.9.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR

- As of Amendment 1, if they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing of the ICF through 4 months after the last dose of study drug, OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only [as of Amendment 1], and lactational amenorrhea [as of Amendment 1] are not acceptable methods of contraception. Female and male condoms should not be used together.)

As of Amendment 1, female patients must agree to not donate eggs (ova) during the course of this study or for 4 months after receiving their last dose of study drug(s).

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, OR

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only [as of Amendment 1], and lactational amenorrhea [as of Amendment 1] are not acceptable methods of contraception. Female and male condoms should not be used together.)

As of Amendment 1, male patients must agree to not donate sperm during the course of this study or for 4 months after receiving their last dose of study drug(s).

6.8.2 Docetaxel

TAXOTERE is a pregnancy Category D drug. Please refer to the TAXOTERE US package insert (USPI) for more information.

> *TAXOTERE can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryofetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryofetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a body surface area basis.*

There are no adequate and well-controlled studies in pregnant women using TAXOTERE. If TAXOTERE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TAXOTERE.[16]

6.8.3 Carboplatin

Carboplatin is a pregnancy Category D drug. Please refer to the Carboplatin Injection USPI for more information.

Carboplatin Injection may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.[17]

6.8.4 Paclitaxel

Paclitaxel is a pregnancy Category D drug. Please refer to the Paclitaxel Injection USPI for more information.

Paclitaxel Injection, USP can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m^2 basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths.

Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m^2 basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If Paclitaxel Injection, USP, is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.[18]

6.8.5 Gemcitabine

Gemcitabine is a pregnancy Category D drug. Please refer to the Gemcitabine USPI for more information.

> *Gemcitabine for injection can cause fetal harm when administered to a pregnant woman. In pre-clinical studies in mice and rabbits, gemcitabine was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of gemcitabine for injection in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.*[(19)]

6.9 Guidance for Clinical Assessment and Management of Hemodynamic Compromise

It is essential that the patient is carefully evaluated at screening and before each MLN4924 dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration.

For those patients for whom there is a concern of dehydration, the following guidance for rehydration before MLN4924 dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate; each infusion of IV fluids should be recorded in the electronic case report forms (eCRFs).

For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL at screening or during the conduct of the study, red blood cell transfusions should be considered before MLN4924 dosing based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines; each red blood cell transfusion should be recorded in the eCRFs. Transfusions should be administered before study drug administration (ie, at least 1 day before dosing).

Patients who experience signs and symptoms of hemodynamic compromise after MLN4924 dosing (eg, tachycardia, hypotension, orthostasis, changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care including hospitalization as clinically indicated.

Patients who experience an untoward reaction with MLN4924 should be followed closely on subsequent dosing.

6.10 Management of Clinical Events

Specific recommendations for the management of MLN4924 clinical events that were identified from toxicology studies in dogs and rats and from early experience in ongoing clinical studies are outlined in the MLN4924 IB and DCSI.

The most common adverse drug reactions for docetaxel, paclitaxel + carboplatin, and gemcitabine are described in Section 1.5. Refer to the applicable USPIs for additional details regarding the management of clinical events attributed to these agents.

Patients who experience an AE with MLN4924 should be followed closely for a recurrence of similar or other AEs upon subsequent dosing of MLN4924.

6.10.1 Guidance for Clinical Assessment and Management of Diarrhea

Diarrhea should be treated promptly with appropriate supportive care, including administration of an antidiarrheal agent according to standard practice or institutional guidelines. Antidiarrheal agents should not be taken prophylactically. Patients should be instructed to begin taking antidiarrheal medication at the first sign of (1) poorly formed or loose stool, (2) occurrence of more bowel movements than usual in 1 day, or (3) unusually high volume of stool. Antidiarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiological specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids to help prevent dehydration.

6.10.2 Guidance for Clinical Assessment and Management of Nausea and Vomiting

Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake. Supportive care with moderate or strong CYP3A4 inhibitors/inducers should be avoided.

6.10.3 Guidance for Use of Granulocyte-Colony Stimulating Factor

Use of growth factors such as granulocyte-colony stimulating factor (G-CSF) during Cycle 1 is permitted for the docetaxel arm but not recommended for the carboplatin, paclitaxel + carboplatin, or gemcitabine arms/cohorts. However, they may be considered for Cycle 2 and beyond, per the investigator's discretion, if there is persistent neutropenia or febrile neutropenia despite dose reductions in the previous course. If G-CSF is used, it

should be used in accordance with the Revised American Society of Clinical Oncology (ASCO) guidelines as published in the Journal of Clinical Oncology (Smith et al, 2006).[23]

6.10.4 Guidance for Clinical Assessment and Management of Anemia

Transfusion and/or erythropoietin may be given as clinically indicated for the treatment of anemia. These should be recorded in the eCRFs.

For all patients with anemia, and especially for patients with hemoglobin values < 9 g/dL at screening or during the conduct of the study, red blood cell transfusions should be considered before MLN4924 dosing based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines; each red blood cell transfusion should be recorded in the eCRFs. Transfusions should be administered before study drug administration (ie, at least 1 day before dosing).

Use of Erythropoietin

Use of erythropoietin during Cycle 1 is not recommended; however, it may be considered in Cycle 2 or beyond, per the investigator's discretion and per institutional guidelines.

6.11 Blinding and Unblinding

This is an open-label study.

6.12 Description of Investigational Agents

6.12.1 MLN4924

The drug product is labeled MLN4924 (MLN4924-003 concentrate for solution for infusion).

The formulation consists of 10 mg/mL MLN4924-003 (as free base) in a solution containing citric acid, sulfobutylether-beta-cyclodextrin, and sodium hydroxide. Each US Pharmacopeia (USP) Type I glass vial nominally contains 5 mL of compounded sterile solution, sealed with a coated butyl rubber stopper, and oversealed with an aluminum seal with a plastic cap.

MLN4924-003 concentrate for solution for infusion Drug Product is formulated with the following excipients: citric acid, sulfobutylether-beta-cyclodextrin, sodium hydroxide, and water for injection.

Details are available in the IB.

6.12.2 Docetaxel

Docetaxel is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the docetaxel prescribing information.

6.12.3 Carboplatin

Carboplatin is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the carboplatin prescribing information.

6.12.4 Paclitaxel

Paclitaxel is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the paclitaxel prescribing information.

6.12.5 Gemcitabine

Gemcitabine is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Please refer to the gemcitabine prescribing information.

6.13 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

MLN4924, docetaxel, paclitaxel, carboplatin, and gemcitabine are anticancer drugs, and as with other potentially toxic compounds, caution should be exercised when handling MLN4924 and chemotherapy agents.

The specified number of MLN4924-003 concentrate for solution for infusion Drug Product vials should be removed and allowed to equilibrate to room temperature before dilution. Using aseptic technique, the specified amount of drug product solution should be removed and administered using a 250 mL 5% dextrose solution. For a detailed preparation of the infusion, refer to the Pharmacy Manual. The MLN4924 (MLN4924-003 concentrate for solution for infusion)-prepared IV bag must be used within 6 hours. The vial must not be

shaken at any time during dose preparation. The bag, needle, and syringe must be disposed of in a proper biohazard container.

Detailed reconstitution and dosage preparation instructions are provided in the Pharmacy Manual.

Please refer to the package inserts for the SoCs (docetaxel, paclitaxel, carboplatin, and gemcitabine) for instructions and precautions regarding preparation.

6.14 Packaging and Labeling

MLN4924 (MLN4924-003 concentrate for solution for infusion) will be provided in 8 or 10 mL USP Type I glass vials nominally containing 5 mL of compounded sterile solution, at a concentration of 10 mg/mL (as free base), sealed with a coated butyl rubber stopper, and oversealed with an aluminum seal with a plastic cap.

Docetaxel, paclitaxel, carboplatin, and gemcitabine may be sourced locally by the clinical sites when arrangements have been made and agreed to by Millennium and the clinical site and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

6.15 Storage, Handling, and Accountability

Vials of MLN4924 (MLN4924-003 concentrate for solution for infusion) are to be stored at 2°C to 8°C.

Please refer to the package inserts for the SoCs (docetaxel, paclitaxel, carboplatin, and gemcitabine) for instructions and precautions regarding preparation.

All investigational supplies are to be kept in a secure area with controlled access.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Disposal instructions are provided in the Pharmacy Manual.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

7.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the contract research organization (CRO) team, and other vendors can be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

The investigator will assign each patient to 1 of the 3 study arms (MLN4924 + docetaxel, MLN4924 + paclitaxel + carboplatin, or MLN4924 + gemcitabine) or the carboplatin lead-in cohort based on his/her medical judgment until enrollment in each arm/cohort is filled.

Patients assigned to the carboplatin lead-in cohort will receive carboplatin in combination with MLN4924. These patients will not enroll in Arm 2 (MLN4924 + paclitaxel + carboplatin).

7.4 Study Procedures

The timing of the study procedures outlined in the following subsections is provided in the Schedules of Events. When applicable, specific visit windows for assessments are provided in the footnotes to the study schedules.

Baseline procedures/tests are to be performed within 3 days before Cycle 1 Day 1. If screening values or results were obtained and acceptable within 3 days before Cycle 1 Day 1, those procedures/tests need not be repeated at Cycle 1 Day 1. Day 1, 3, 5, 8, or 15 dosing (of any cycle) may be delayed by up to 2 days (Cycles 1 through 12) or up to 2 weeks (after completion of Cycle 12; up to 4 weeks after consulting with the sponsor) to

accommodate inclement weather, holidays, vacations, or other administrative reasons; treatment breaks may not be taken consecutively.

Refer to the following Schedules of Events for timing of assessments.

Cycle 1 Only

- Cycle 1: Arm 1 and Arm 2
- Cycle 1: Arm 3

Cycle 2 and Beyond

- Cycle 2 and Beyond: Arm 1, and Cycle 2 through Cycle 12: Arm 2
- Cycle 13 and Beyond: Arm 2 (as of Amendment 1)
- Cycle 2 and Beyond: Arm 3

Dose Escalation Phase

- Cycle 1: Arm 1 Dose Escalation Pharmacokinetics Schedule
- Cycle 1: Arm 2 Dose Escalation Pharmacokinetics Schedule
- Cycle 1: Arm 3 Dose Escalation Pharmacokinetics Schedule

MTD Expansion Phase

- Cycle 1: Arm 1 Maximum Tolerated Dose Expansion Pharmacokinetics Schedule
- Cycle 1: Arm 2 MTD Expansion Pharmacokinetics Schedule
- Cycle 1: Arm 3 MTD Expansion Pharmacokinetics Schedule

Additional details are provided as necessary in the sections that follow.

7.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

7.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening (within 28 days before the first dose of any study drug).

7.4.3 Medical History

During screening, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it (see inclusion criterion 3, Section 5.1). Concomitant medications will be recorded as specified in Section 7.4.11.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedules of Events.

Symptom-directed physical examinations will also be conducted at times specified in the Schedules of Events.

7.4.5 Patient Height

Height will be measured during screening only.

7.4.6 Patient Weight

Weight will be measured before MLN4924 dosing as indicated in the Schedules of Events.

7.4.7 Eastern Cooperative Oncology Group Performance Status

ECOG PS (Section 15.3) will be assessed as indicated in the Schedules of Events.

7.4.8 Echocardiogram

LVEF should be assessed by echocardiogram or radionuclide angiography at screening.

7.4.9 Vital Signs

Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected as indicated in the Schedules of Events and as clinically indicated. All of these measurements are taken with the patient in a sitting position (and/or supine after completion of Cycle 12) as noted in the Schedules of Events.

At predose and 1 hour postdose of MLN4924 administration on Cycle 1 Day 1, orthostatic blood pressure and heart rate measurements will be taken with the patient in a supine position and then standing, after waiting for approximately 3 to 4 minutes.

7.4.10 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. The results from these tests must be available and negative before the first dose of study drug.

7.4.11 Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded from the time of the first dose of any study drug through 30 days (+ 10 days) after the last dose of study drug(s). See Section 6.6 and Section 6.7 for additional details regarding excluded and permitted concomitant medications and procedures.

7.4.12 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedules of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

7.4.13 Enrollment

Enrollment is achieved when the first dose of any study drug has been administered.

Procedures for completion of the enrollment information are described in the Pharmacy and Study Manuals.

7.4.14 Electrocardiogram

A 12-lead ECG will be performed as indicated in the Schedules of Events.

The ECGs performed after infusion should be reviewed by the investigator or his/her delegate before the patient leaves the clinic.

7.4.15 Clinical Laboratory Evaluations

Hematology, Clinical Chemistry, Coagulation, Urinalysis, and Urine Safety Assessment

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedules of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet (count)
- Leukocytes with differential
- Neutrophils (ANC)

Serum Chemistry

- Blood urea nitrogen (BUN)
- Creatinine
- Bilirubin (total)
- Direct bilirubin
- Urate
- Lactate dehydrogenase (LDH)
- Gamma glutamyl transferase (GGT)[a]
- Phosphate
- Albumin
- ALP
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium

a No longer required after completion of Cycle 12 (as of Amendment 1).

Coagulation

Screening

- PT (international normalized ratio [INR])
- aPTT
- Fibrinogen
- D-dimer

Cycle 1 and Beyond

- PT (INR)
- aPTT

If the initial coagulation screen is positive, follow-up coagulation studies should include a full coagulation panel rather than PT (INR)/aPTT alone. If the initial coagulation screen is negative, follow-up coagulation studies should include only PT (INR) and aPTT.

Urinalysis With Microscopic Analysis

- Turbidity and color
- pH
- Specific gravity
- Protein
- Ketones[a]
- Bilirubin[a]
- Occult blood
- Nitrite
- Urobilinogen[a]
- Glucose[a]
- Leukocytes
- Microscopic assessment

a Removed after completion of Cycle 12 (as of Amendment 1).

Urine Safety Assessment[a]

- Albumin
- Creatinine
- Phosphate
- Kidney injury molecule-1

a Removed after completion of Cycle 12 (as of Amendment 1).

7.4.16 Disease Assessment

CT scans with IV contrast (unless medically contraindicated) of the chest, abdomen, and pelvis will be performed during screening. CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter (Cycles 4-12) or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 1), and at the EOS visit. Additional CT scans may be performed, per the investigator's discretion, if clinically indicated. If CT scan does not provide adequate imaging, MRI may be used to evaluate sites of disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1 Day 1, then the results of those scans may be used for the screening assessment. For each site of disease, the imaging modality (CT or MRI) used at screening must be used throughout the study. Tumor response will be assessed by the investigator at these times using RECIST, version 1.1.[(22)]

7.4.17 Tumor Biopsies

Tumor biopsy is not required in this study for patients with adequate archived tumor material. Banked paraffin-embedded tumor tissue or a minimum of 10 unstained slides of the tumor tissue is required for study entry and will be collected at screening to enable genetic characterization of the tumor CCI [redacted] In the event that no banked tumor tissue or archived slides are available, a fresh tumor biopsy will be required before enrollment in this study.

7.4.18 Pharmacokinetic Measurements

Blood samples for the determination of MLN4924 plasma concentrations and, if appropriate, its metabolites, will be collected only during Cycle 1 of treatment. The timing, but not the number, of PK blood samples may be changed if emerging data indicate that an alteration in sampling scheme is needed to better characterize the PK of MLN4924. To ensure that the measurements are representative of plasma exposure, blood draws will be conducted in the arm opposite to a patient's IV infusion. In the case that only a single arm is available, blood should be drawn as distal to the site of IV infusion as feasible, and the site of blood draw should be documented.

Dose Escalation Phase

During the dose escalation portion of the study (excluding the Arm 2 carboplatin lead-in cohort), blood samples will be collected from each patient for the determination of MLN4924 plasma concentrations during the first cycle of treatment at the time points indicated in the Schedules of Events.

The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion.

MTD Expansion Phase

During the MTD expansion portion of the study, serial blood samples will be collected from all patients at the time points indicated in the Schedules of Events before and after the start of MLN4924 infusion. The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion.

Details regarding the preparation, handling, and shipping of samples are provided in the Study Manual.

For patients who experience hypersensitivity or a hepatic, cardiac, or renal SAE considered by the investigator to be at least possibly related to study drug, an additional blood sample should be collected, if clinically feasible, for the determination of MLN4924 plasma concentration as close to the onset of the event as possible.

If deemed appropriate, the blood samples collected in this study may be additionally analyzed to determine plasma concentrations of MLN4924 major metabolites in humans.

7.4.19 Whole Blood Sample for Genomic DNA

During screening, a blood sample will be collected for generation of genomic DNA for interpretation of the presence of somatic DNA mutations. These samples will be retained until drug is approved by regulatory authorities or discontinuation of the MLN4924 program; if at that time they have not been consumed during research, they will be destroyed.

7.4.20 Banked Tumor Specimen Measurements

Banked paraffin-embedded tumor tissue or a minimum of 10 unstained slides of the tumor tissue (ie, tumor tissue obtained at the time of the patient's original diagnosis and/or at the time of subsequent procedures conducted as part of the patient's standard care) will be collected CCI [redacted]

7.4.21 Plasma Sample Collection

During screening, a blood sample will be collected to generate a plasma sample CCI [redacted]

7.5 Completion of Study

Patients will be considered to have completed the study if they discontinue treatment for any of the reasons outlined in Section 7.6.

7.6 Discontinuation of Treatment with Study Drug, and Patient Replacement

Treatment with study drug may be discontinued for any of the following reasons:

- AE
- Protocol violation
- PD

- Symptomatic deterioration
- Unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

Once study drug has been discontinued, all study procedures outlined for the EOS visit will be completed as specified in the Schedules of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

For determination of the MTD in the dose escalation phase, patients will be replaced if withdrawn from treatment during Cycle 1 for reasons other than DLT.

Note: Patients may receive MLN4924 until they experience PD or unacceptable MLN4924-related toxicities. The maximum duration of treatment will be 12 cycles; however, if it is determined after discussion between the investigator and the sponsor that a patient would derive benefit from continued treatment, the patient may remain on combination therapy (MLN4924 + SoC) or receive MLN4924 as a single agent beyond 12 cycles.

Patients who are resistant to the SoC AND who have achieved objective clinical benefit from combination therapy (SoC plus MLN4924) AND who have developed intolerance that is reasonably attributable to the SoC after 4 or more cycles may continue on single-agent MLN4924 under these circumstances at the same dose and schedule upon request by the investigator and agreement by the sponsor.

7.7 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

Statistical analyses will be primarily descriptive and graphical in nature. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan (SAP) will be developed and finalized before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.1 Determination of Sample Size

It is anticipated that approximately 69 patients will be enrolled combining the dose escalation for the determination of MTD for each combination, the cohort expansion at each MTD, and estimating approximately 6 patients enrolled in the carboplatin lead-in cohort.

An adaptive approach using a Bayesian CRM will be used for dose escalation. Based on the observed toxicities in the DLT-evaluable population (Section 8.1.3), the CRM algorithm will predict the MTD of MLN4924 with SoC, defined as the dose level closest to that predicted to result in a DLT rate of 25%, also known as the target toxicity rate. The dose toxicity relationship is modeled by a single-parameter (α) logistic model. Table 8-1 shows the operating characteristics of the CRM using Monte Carlo simulations versus the traditional "3 + 3" escalations rules for several assumptions of the true MTD.

Table 8-1 Operating Characteristics of Continual Reassessment Method Versus Traditional Escalation Rules ("3 + 3")

Scenario	Dose Levels (mg/m^2)	True DLT Rate	Method	MTD Median (P5, P95)	Accuracy Rate (%)[a]	Number of Patients Median (P5, P95)	Number of DLTs Median (P5, P95)
1	15; 25; 37; 50	0.10; 0.15; 0.20; 0.25	CRM	37 (15, 50)	65.76	15 (8, 21)	2 (1, 4)
			3 + 3	37 (0, 50)	50.88	15 (6, 21)	2 (1, 4)
2	15; 25; 37; 50	0.20; 0.25; 0.30; 0.35	CRM	25 (0, 50)	64.12	12 (3, 21)	3 (2, 5)
			3 + 3	15 (0, 50)	62.16	12 (3, 21)	3 (2, 5)
3	15; 25; 37; 50	0.40; 0.45; 0.50; 0.55	CRM	0 (0, 25)	---	6 (3, 15)	3 (2, 6)
			3 + 3	0 (0, 25)	---	6 (3, 15)	2 (2, 5)
4	25; 50; 75; 100	0.10; 0.15; 0.20; 0.25	CRM	75 (25, 100)	65.82	15 (8, 21)	2 (1, 5)
			3 + 3	75 (0, 100)	50.88	15 (6, 21)	2 (1, 4)

Table 8-1 Operating Characteristics of Continual Reassessment Method Versus Traditional Escalation Rules ("3 + 3")

Scenario	Dose Levels (mg/m^2)	True DLT Rate	Method	MTD Median (P5, P95)	Accuracy Rate (%)[a]	Number of Patients Median (P5, P95)	Number of DLTs Median (P5, P95)
5	25; 50; 75; 100	0.20; 0.25; 0.30; 0.35	CRM	50 (0, 100)	63.68	12 (3, 21)	3 (2, 5)
			3 + 3	25 (0, 100)	62.16	12 (3, 21)	3 (2, 5)
6	25; 50; 75; 100	0.40; 0.45; 0.50; 0.55	CRM	0 (0, 50)	---	6 (3, 15)	3 (2, 6)
			3 + 3	0 (0, 50)	---	6 (3, 15)	2 (2, 5)

Abbreviations: CRM=continual reassessment method; DLT=dose-limiting toxicity; 3 + 3=traditional "3 + 3" escalation rules; MTD=maximum tolerated dose; P5=5th percentile; P95=95th percentile.

a Accuracy rate is defined as the proportion of simulated trials that identify the MTD as a dose with true DLT rate within the interval (0.20, 0.30). Results are based on 5000 simulations per scenario.

In all scenarios, the CRM and 3 + 3 designs require similar numbers of patients and yield similar numbers of total DLTs. The CRM design generally yields a higher accuracy rate in predicting the MTD.

The starting dose for Arms 1 and 2 will be 15 mg/m^2, and the starting dose for Arm 3 will be 25 mg/m^2. The intervals between dose levels are prespecified and are not determined by the CRM algorithm. For Arms 1 and 2, the increases will be approximately 1.67-, 1.5-, and 1.33-fold over the previous dose level, and for Arm 3, the increases will be 2-, 1.5, and 1.33-fold over the previous dose level (as described in Table 6-2). After the first 3 patients are dosed and have completed Cycle 1, the CRM algorithm will be updated based on the observed DLTs, and the PMTD will be calculated. The dose escalation rules are specified in Section 6.4. When the total number of patients in a dose level reaches at least 6 and the algorithm does not recommend escalation or de-escalation, that dose level may be considered the MTD. Based on an estimated toxicity rate of 25% at 50 mg/m^2 in Arms 1 and 2 and at 100 mg/m^2 in Arm 3 (Scenarios 1 and 4 in Table 8-1), computer simulations estimate that approximately 15 patients will be enrolled in each arm to determine the MTD of MLN4924 with SoC.

Once each MTD is determined, approximately 6 additional patients (MTD expansion cohort) will be enrolled in each arm such that a total of approximately 12 patients will be enrolled and treated at each MTD to more fully characterize the safety, tolerability, and PK of MLN4924 with SoC. These enrollment rules are based on the binomial probability

assumption that if a particular toxicity occurs in 12.5% of the entire patient population, there is an 80% probability of observing at least 1 occurrence of that toxicity in 12 patients.

8.1.2 Randomization and Stratification

Patients will be enrolled according to the CRM, as described in Section 6.4 and Figure 6-1. No randomization is planned for this study.

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- **Safety Population**: The Safety population is defined as all patients who receive at least 1 dose of any study drug.
- **Response-Evaluable Population**: The Response-Evaluable population is defined as all patients who receive at least 1 dose of study drug, have measurable disease at baseline, and have at least 1 postbaseline disease assessment.
- **PK Population**: The PK population is defined as all patients who have concentration–time data to reliably estimate PK parameters.
- **DLT-Evaluable Population**: The DLT-Evaluable population is defined as all patients who either experience DLT during Cycle 1 or receive all scheduled doses of study drug during Cycle 1 without DLT. Patients in Arm 3 will still be considered DLT evaluable if they receive gemcitabine on Days 1 and 8 only or on Days 1 and 15 only.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available safety and efficacy data will be included in data listings and tabulations. No imputation of values for missing data will be performed. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including gender, age, race, weight, height, BSA, primary diagnosis, and other parameters as appropriate will be summarized. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

Analysis of all efficacy measures will be descriptive. Disease response to MLN4924 in combination with SoC will be based on the best overall response as determined by the investigator using RECIST version 1.1 guidelines (Section 15.2).[22] The duration of response will be defined in patients with disease response (CR or PR) as the time between the first documentation of response and PD. Responders without PD will be censored at the last clinical assessment of response.

8.1.7 Pharmacokinetics and Biomarkers

Pharmacokinetic Analysis

All individual concentration–time data will be pooled to describe the population PK of MLN4924. As data permit, a nonlinear regression mixed effects model (NONMEM software) will be used to assess MLN4924 exposure when administered in combination with the selected SoC therapies. Individual metabolite data may also be assessed, as deemed appropriate. If appropriate, historical data may be used in this analysis to increase the robustness of the model and precision of estimated PK parameters and compare with single-agent data. Details of the modeling approach will be provided in a separate analysis plan, and the results of these analyses will be reported separately.

As data permit, individual and mean MLN4924 plasma concentration–time data will be tabulated and plotted for each combination therapy.

Biomarkers

CCI

8.1.8 Safety Analysis

The incidence of DLT will be tabulated for each dose group. In addition, to assess the relationship between toxicities and MLN4924 dose, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group. The DLT-Evaluable population will be used for the analysis of DLT.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and changes from baseline in the patient's vital signs, weight, physical examination findings, ECG results, and clinical laboratory results using the Safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients)
- SAEs

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the MLN4924 safety profile.

Descriptive statistics for the actual values and changes from baseline in ECGs will be tabulated by time point, including any unscheduled measurements.

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (WHO) drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of MLN4294.

8.1.9 Interim Analysis

No formal interim analysis is planned for this study.

9. STUDY COMMITTEES

9.1 Millennium Safety Assessments

Safety data will be reviewed and assessed periodically by a Global Pharmacovigilance team and a cross-functional Safety Management Team throughout the conduct of the study. These cross-functional reviews will include a Global Safety Lead from the study team, as well as other representation from other departments at Millennium such as Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[(1)] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

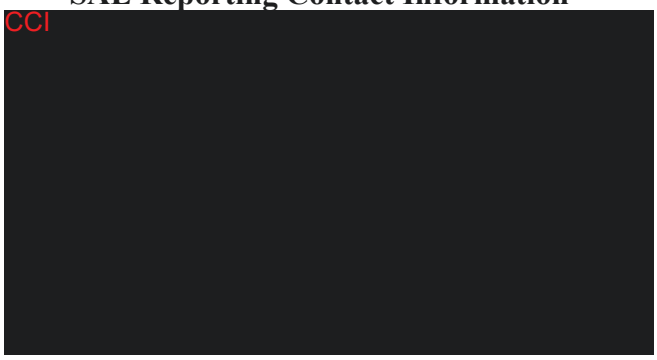
10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

CCI



Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[(1)] The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from first dose of any study drug through 30 days (+ 10 days) after administration of the last dose of study drug and recorded in the eCRFs.
- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium Department of Pharmacovigilance or designee from the first dose of study drug through 30 days (+ 10 days) after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

Millennium, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium,

or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email address provided below. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Call Center	Phone Number	Email	Fax
Dohmen Life Science Services (DLSS)	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to CCI (refer to Section 10.2).

11.12 Closure of the Study

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

11.13 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and Millennium notified.

12. USE OF INFORMATION

All information regarding MLN4924 supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN4924 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

13. INVESTIGATOR AGREEMENT

I have read Protocol C15010 Amendment 1: A Phase 1b, Open-Label, Dose Escalation, Multi-arm Study of MLN4924 Plus Docetaxel, Gemcitabine, or Combination of Carboplatin and Paclitaxel in Patients With Solid Tumors

I agree to conduct the study as detailed herein and in compliance with International Council for Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Hematologic Toxicity of Carboplatin Alone and in Combination With Paclitaxel

In 2 prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Southwest Oncology Group (SWOG), 789 chemotherapy-naïve patients with advanced ovarian cancer were treated with carboplatin or cisplatin in combination with cyclophosphamide every 28 days for 6 courses before surgical reevaluation. See Table 15-1 for the hematologic adverse experiences of patients treated with carboplatin.

Table 15-1 Hematologic Adverse Experiences of in Patients With Ovarian Cancer Treated With Carboplatin or Cisplatin in Combination With Cyclophosphamide

Adverse Experience	Laboratory Value	NCIC CTG Study % Patients (N=447)	SWOG Study % Patients (N=342)
Bone Marrow			
Thrombocytopenia	< 1000,000/mm^3	70	59
	< 50,000/mm^3	41	22
Neutropenia	< 2000 cells/mm^3	97	95
	< 1000 cells/mm^3	81	84
Leukopenia	< 4000 cells/mm^3	98	97
	< 2000 cells/mm^3	68	76
Anemia	< 11 g/dL	91	88
	< 8 g/dL	18	8
Infections		14	18
Bleeding		10	6
Transfusions		42	25

Abbreviations: NCIC CTG=National Cancer Institute of Canada Clinical Trials Group; SWOG=Southwest Oncology Group.
Source: Carboplatin US Package Insert [17]

In a randomized clinical trial, 798 patients with ovarian cancer were treated with either cisplatin/paclitaxel or paclitaxel/carboplatin therapy at 3-week intervals for 6 courses. See Table 15-2 for the hematologic adverse experiences of patients treated with paclitaxel/carboplatin.

Table 15-2 Hematologic Toxicities and Associated Supportive Care in Patients With Advanced Ovarian Cancer Stratified by Treatment Arm and Toxicity Grade

		NCI CTC Grade, %												Difference[a] in the Proportions of Patients With Grades 3/4 Toxicity, %	
		Paclitaxel/Carboplatin Arm						Cisplatin/Paclitaxel Arm							
Toxicity	**Set**	**N**	**0**	**1**	**2**	**3**	**4**	**N**	**0**	**1**	**2**	**3**	**4**	**E**	**95% CI**
Hemoglobin	C	2209	29.1	49.4	20.1	1.3	0.1	2095	33.6	49.5	16.1	0.8	0.0	-0.6	-1.3 to 0.0
	P	388	9.0	40.7	44.3	5.4	0.5	382	14.7	44.2	37.2	3.9	0.0	-2.0	-5.1 to 1.1
Platelets	C	2193	71.9	19.9	5.2	2.5	0.5	2082	93.4	6.2	0.2	0.2	0.0	**-2.9**	**-3.6 to -2.1**
	P	388	43.3	31.2	12.6	10.1	2.8	382	78.3	19.4	1.3	1.0	0.0	**-11.8**	**-15.3 to -8.4**
Transfusions pRBCs[a]	C	1868	94.3	--	--	5.7	--	1766	97.2	--	--	2.8	--	**-2.9**	**-4.2 to -1.6**
	P	383	81.7	--	--	18.3	--	370	89.5	--	--	10.5	--	**-7.7**	**-12.7 to -2.8**
Leukocytes	C	2200	37.0	22.6	29.3	10.8	0.3	2073	56.4	23.3	17.3	2.9	0.0	**-8.1**	**-9.6 to -6.6**
	P	388	13.4	16.0	38.7	30.4	1.5	382	31.4	35.1	32.7	10.5	0.3	**-21.2**	**-26.8 to -15.6**
Neutrophils	C	1842	56.9	12.9	12.8	12.4	5.0	1864	70.9	10.6	9.8	6.4	2.3	**-8.7**	**-10.8 to -6.5**
	P	371	31.3	12.9	18.9	21.6	15.4	373	48.0	13.1	16.9	15.0	7.0	**-14.9**	**-21.4 to -8.5**
Febrile neutropenia	C	2228	98.3	--	--	1.7	0.0	2110	99.3	--	--	0.7	0.0	**-0.9**	**-1.6 to -0.3**
	P	388	92.0	--	--	8.0	0.0	384	96.4	--	--	3.6	0.0	**-4.3**	**-7.6 to -1.1**
Supportive care: antibiotics[b]	C	1868	98.3	--	--	1.7	--	1768	97.9	--	--	2.1	--	0.4	-0.5 to 1.3
	P	383	93.2	--	--	6.8	--	370	90.5	--	--	9.5	--	2.7	-1.2 to 6.6
Supportive care: G-CSF[b]	C	1868	94.0	--	--	6.0	--	1767	98.2	--	--	1.8	--	-4.2	**-5.5 to -3.0**
	P	383	85.6	--	--	14.4	--	370	95.4	--	--	4.6	--	-9.8	**-13.9 to -5.7**

Table 15-2 Hematologic Toxicities and Associated Supportive Care in Patients With Advanced Ovarian Cancer Stratified by Treatment Arm and Toxicity Grade

Source: du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95(17):1320-9.[24]

Abbreviations: --=not defined; C=maximum grade over all courses; CI=confidence interval; G-CSF=granulocyte colony-stimulating factor; E=estimate; N=number of courses in set C and number of patients in set P; NCI CTC=National Cancer Institute Common Toxicity Criteria; P=maximum grade over all courses within a patient; pRBCs=packed red blood cells.

a Differences are calculated by subtracting the paclitaxel/carboplatin arm proportion from the cisplatin/paclitaxel arm proportion; statistically significant differences in proportions between the 2 treatment arms are bold. All percentages are rounded; therefore, the estimates may differ by ± 1 from the difference of the percentages of the treatment arm columns.

b Transfusion of pRBCs, use of antibiotics, and G-CSF were not assessed for the last treatment cycle within a patient. Use of antibiotics and G-CSF is graded in the same fashion as transfusion of pRBCs. Use of antibiotics/application of G-CSF is coded as a toxicity of Grade 3; a Grade 0 is applied otherwise.

15.2 Response Criteria

Disease Response Criteria for Target and Nontarget Lesions

Evaluation of Target Lesions	
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Evaluation of Nontarget Lesions	
Complete Response (CR)	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45 (2): 228-47.[(22)]

Overall Disease Response Criteria

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45 (2): 228-47.[(22)]

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.

15.3 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[25]

15.4 Formula for Absolute Neutrophil Count Calculation

ANC=total leukocyte count × total percentage of neutrophils (segmented neutrophils + band neutrophils)

Example:

If: total leukocyte count=4.3; segmented neutrophils=48%; band neutrophils=2%

Then: 4300 × (0.48 + 0.02)=4300 × 0.5=ANC of 2150

15.5 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})} \text{ OR } \frac{(140 - \text{age [years]}) \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = 0.85 \frac{(140 - \text{age[years]}) \times \text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})} \text{ OR } 0.85 \frac{(140 - \text{age[years]}) \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

15.6 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.[26]

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

15.7 Excluded CYP3A Inducers

Note that HIV medications that are strong CYP3A inducers are not included in this list because HIV-positive patients are excluded from study participation.

Use of the clinically significant CYP3A inducers listed in Table 15-3 should be avoided during MLN4924 therapy.

Table 15-3 In Vivo Inducers of CYP3A

Strong Inducers ≥ 80% Decrease in AUC	Moderate Inducers 50%-80% Decrease in AUC
Carbamazepine	Bosentan
Phenytoin	Efavirenz
Phenobarbital	Modafinil
Primidone	Nafcillin
Rifabutin	
Rifampin	
Rifapentine	
St. John's Wort	

Abbreviations: AUC=area under the plasma concentration versus time curve; CYP=cytochrome P450.
This is not an exhaustive list; please refer to the following sources:
medicine.iupui.edu/flockhart/table.htm and
fda.gov/CDER/drug/drugInteractions/tableSubstrates.htm for additional information

15.8 Drugs Associated with Nephrotoxicity

The drugs listed in Table 15-4 are permitted to be used during the conduct of this study but should be used with caution.

Table 15-4 Drugs Associated with Nephrotoxicity

Analgesics	Cardiovascular agents
Nonsteroidal anti-inflammatory drugs	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
Antidepressants/mood stabilizers	Clopidogrel (Plavix), ticlopidine (Ticlid)
Lithium	Contrast dye
Antimicrobials	Diuretics
Acyclovir (Zovirax)	Loops, thiazides
Aminoglycosides	Triamterene (Dyrenium)
Amphotericin B (Fungizone; deoxycholic acid formulation more so than the lipid formulation)	Herbals
Beta lactams (penicillins, cephalosporins)	Chinese herbals with aristocholic acid
Foscarnet (Foscavir)	Others
Ganciclovir (Cytovene)	Allopurinol (Zyloprim)
Pentamidine (Pentam)	Gold therapy
Quinolones	Haloperidol (Haldol)
Rifampin (Rifadin)	Pamidronate (Aredia)
Sulfonamides	Phenytoin (Dilantin)
Vancomycin (Vancocin)	Quinine (Qualaquin)
Antiretrovirals	Zoledronate (Zometa)
Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	
Indinavir (Crixivan)	
Calcineurin inhibitors	
Cyclosporine (Neoral)	
Tacrolimus (Prograf)	

Source: Modified from Naughton et al, 2008.[27]

15.9 Methods of Contraception Considered to be Effective

Acceptable Contraception Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered to be highly effective. Such methods include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[a]:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - Oral.
  - Injectable.
  - Implantable.[b]
- Intrauterine device.[b]
- Intrauterine hormone-releasing system.[b]
- Bilateral tubal occlusion.[b]
- Vasectomised partner.[b,c]
- Sexual abstinence.[d]

Contraception Methods Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.[e]
- Cap, diaphragm, or sponge with spermicide.[e]

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which

may reduce the efficacy of the contraception method.
[b] Contraception methods that in the context of this guidance are considered to have low user dependency.
[c] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.
[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective birth control methods.

15.10 Amendment 1 Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 1 are indicated. The corresponding text has been revised throughout the protocol. All changes are applicable after completion of Cycle 12.

Change 1: Extend the 2-day window for scheduling issues (eg, inclement weather, holidays, vacations, or other administrative reasons) to 2 weeks; treatment breaks of up to 4 weeks may be permitted after discussion between the investigator and the project clinician or designee, and the investigator will confirm patient eligibility for continued treatment upon return, before treatment.

The primary change occurs in: Section 6.5 Dose-Modification Guidelines (Dose Delays, Dose Reductions, and Dose Interruptions):

Added text: **For patients who take treatment breaks at the investigator's discretion, patient eligibility for continued treatment, including all Day 1 predose assessments specified in the Schedules of Events, will be confirmed by the investigator before resuming treatment. Treatment breaks must be no longer than 2 weeks in duration (extended up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively.**

Rationale for Change:

The visit window for assessments was extended to 2 weeks to accommodate scheduling issues, and an option for treatment breaks (up to 4 weeks after consulting with the sponsor) was added to allow flexibility for patients continuing beyond 12 cycles of treatment.

The following sections also contain this change:

- Section 4.1 Overview of Study Design.
- Section 4.3 Duration of Study.
- Section 6.1 Study Drug Administration.
- Section 7.4 Study Procedures.

Change 2: Reduce the frequency of disease response assessments from every 3 cycles to every 6 cycles.

The primary change occurs in Section 7.4.16 Disease Assessment:

Added text: CT scans with IV contrast encompassing the known sites of disease will be performed at the end of Cycle 2 and then every other cycle thereafter **(Cycles 4-12) or after completion of every sixth cycle after the patient's previous scan (after completion of Cycle 12 and implementation of Amendment 1)**, and at the EOS visit. **Additional CT scans may be performed, per the investigator's discretion, if clinically indicated.**

Rationale for Change:

The reduction in frequency of disease response assessments was made to lessen the burden for patients continuing beyond 12 cycles of treatment.

The following sections also contain this change:

- Protocol Summary.
- Schedules of Events: Cycle 13 and Beyond: Arm 2 (as of Amendment 1).
- Section 4.1 Overview of Study Design.

Change 3: Reduce the frequency of hematology and clinical chemistry assessments and physical examinations.

The primary change occurs in Schedules of Events: Cycle 13 and Beyond: Arm 2 (as of Amendment 1):

Description of change:	Day 8 and 15 hematology, clinical chemistry, and symptom-directed physical examination are not present in the new Schedule of Events for Cycle 13 and Beyond. As these were the only activities on Days 8 and 15, the clinic visits on these dates are not present in the new Schedule of Events. The complete physical examination on Day 1 was also replaced with a symptom-directed physical examination.

Rationale for Change:

The Day 8 and 15 hematology assessment, clinical chemistry panel, and symptom-directed physical examination and the Day 1 complete physical examination are not present in the new Schedule of Events for Cycle 13 and beyond because these assessments are no longer considered necessary for patients continuing beyond 12 cycles of treatment; on Day 1, a symptom-directed physical examination is considered sufficient.

Change 4: Remove ketones, bilirubin, urobilinogen, and glucose from the Urinalysis With Microscopic Analysis parameters.

The primary change occurs in Section 7.4.15 Clinical Laboratory Evaluations:

Description of change:	Ketones, bilirubin, urobilinogen, and glucose have been removed from the Urinalysis With Microscopic Analysis parameters after completion of Cycle 12.

Rationale for Change:

These changes to the urinalysis parameters were made to be consistent with program-wide recommendations.

Change 5: Add a ±10-minute window to the MLN4924 infusion duration.

The primary change occurs in Section 6.1.1 MLN4924 Administration:

Initial wording:	Patients will receive MLN4924 diluted with 5% dextrose in a 250-mL bag via a 60-minute IV infusion… The entire content of the MLN4924 IV bag will be infused at a constant rate over 1 hour.
Amended new wording:	Patients will receive MLN4924 diluted with 5% dextrose in a 250-mL bag via a ~~60-minute~~ **1-hour (±10 minutes as of Amendment 1)** IV infusion… The entire content of the MLN4924 IV bag will be infused at a constant rate over 1 hour **(±10 minutes as of Amendment 1)**.

Rationale for Change:

The addition of the ±10-minute window to the MLN4924 infusion duration was made to allow flexibility in MLN4924 infusion duration.

Change 6: Remove the requirement for independent data monitoring committee monitoring.

The primary change occurs in deleted Section 9.2 Independent Data Monitoring Committee:

Deleted text:	~~9.2 Independent Data Monitoring Committee~~ ~~An IDMC has been formed to periodically monitor the overall conduct of studies within the MLN4924 program, including review of accumulating clinical study data and safety data (both clinical and nonclinical) and to make recommendations to Millennium to safeguard the interests of study participants. Additionally, the IDMC may make recommendations relating to the selection/recruitment/retention of study participants, patient management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. Further details regarding the IDMC are located in the IDMC charter.~~

Rationale for Change:

No new safety issues were identified from Study C15010 data analyzed during independent data monitoring committee meetings, and only 2 patients remain active in the study; therefore, as of Amendment 1 implementation, the independent data monitoring committee will no longer be required to monitor Study C15010.

Section 1.5.1 Risks of MLN4924 Therapy also contains this change.

Change 7: Adjust contraception requirements to be consistent with Clinical Trial Facilitation Group recommendations.

The primary change occurs in Section 6.8.1 MLN4924:

Initial wording:

6.8.1 MLN4924

Female patients must meet 1 of the following:

…

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form (ICF) through 4 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

…

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

Amended or new wording:

6.8.1 MLN4924

Female patients must meet 1 of the following:

…

- **As of Amendment 1,** ~~I~~if they are of childbearing potential, agree to practice ~~2~~ **1 highly** effective method~~s~~ **and 1 additional effective (barrier) method** of contraception**, at the same time,** from the time of signing the ~~informed consent form~~ **ICF** through ~~30 days~~ **4 months** after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the ~~subject~~ **patient**. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], ~~and~~ withdrawal**, spermicides only [as of Amendment 1], and lactational amenorrhea [as of Amendment 1]** are not acceptable methods of contraception. **Female and male condoms should not be used together.**)

As of Amendment 1, female patients must agree to not donate eggs (ova) during the course of this study or for 4 months after receiving their last dose of study drug(s).

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

…

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the ~~subject~~ **patient**. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods for the female partner], ~~and~~ withdrawal**, spermicides only [as of Amendment 1], and lactational amenorrhea [as of Amendment 1]** are not acceptable methods of contraception. **Female and male condoms should not be used together.**)

As of Amendment 1, male patients must agree to not donate sperm during the course of this study or for 4 months after receiving their last dose of study drug(s).

Rationale for Change:

The update in contraception requirements was included for consistency with program-wide updates.

The following sections also contain this change:

- Section 5.1 Inclusion Criteria.
- New Section 15.9 Methods of Contraception Considered to be Effective.

Change 8: Update the description of the drug product.

The primary change occurs in Section 6.14 Packaging and Labeling:

Initial wording:	MLN4924 (MLN4924-003 Injection) will be provided in 10-mL USP Type I glass vials nominally containing 5 mL of compounded sterile solution, at a concentration of 10 mg/mL (as free base), sealed with a coated butyl rubber stopper, and oversealed with an aluminum seal with a plastic cap.
Amended or new wording:	MLN4924 (MLN4924-003 ~~Injection~~**concentrate for solution for infusion**) will be provided in **8 or** 10 mL USP Type I glass vials nominally containing 5 mL of compounded sterile solution, at a concentration of 10 mg/mL (as free base), sealed with a coated butyl rubber stopper, and oversealed with an aluminum seal with a plastic cap.

Rationale for Change:

The update of drug product description was an administrative change in response to the new, program-wide description for the drug product.

The following sections also contain this change:

- Section 6.12.1 MLN4924.
- Section 6.13 Preparation, Reconstitution, and Dispensation.
- Section 6.15 Storage, Handling, and Accountability.

Change 9: Update the investigator responsibilities for compliance with updated International Council for Harmonisation guidelines.

The primary change occurs in Section 11.1 Good Clinical Practice:

Added Text: **The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.**

Rationale for Change:

Investigator responsibilities were updated to comply with updated changes in ICH guidelines.

Change 10: Update the description of the dose-limiting toxicity observed in Study C15003 to be consistent with final data.

The primary change occurs in Section 1.3 Clinical Experience:

Initial wording: The maximum tolerated dose (MTD) for Schedule A was established at 59 mg/m^2 based on dose-limiting toxicities (DLTs) of increased transaminases and shock observed at a dose level of 79 mg/m^2.

Amended or new wording: The maximum tolerated dose (MTD) for Schedule A was established at 59 mg/m^2 based on **a** dose-limiting toxicity~~ies~~ (DLT~~s~~) of increased transaminases ~~and shock~~ observed at a dose level of ~~79~~ **78** mg/m^2.

Rationale for Change:

The description of the DLT observed in Study C15003 was updated to be consistent with the final data presented in the IB and clinical study report.

Change 11: Update vital signs assessments to allow measurements to be taken with the patient in the supine or sitting position.

The primary change occurs in Section 7.4.9 Vital Signs:

Added text: Vital signs, including diastolic and systolic blood pressure, heart rate, and body temperature will be collected as indicated in the Schedules of Events and as clinically indicated. All vital signs will be measured in the sitting position **(and/or supine after completion of Cycle 12) as noted in the Schedules of Events.**

Rationale for Change:

Supine vital signs assessments are permitted after completion of Cycle 12, consistent with program-wide recommendations.

The Schedules of Events: **Cycle 13 and Beyond: Arm 2 (as of Amendment 1)** also contains this change.

Change 12: Clarify that if needed, a red blood cell transfusion must occur at least 1 day before study drug administration.

The primary change occurs in Section 6.7 Permitted Concomitant Medications and Procedures:

Added text: Red blood cell transfusions must be administered before administration of study drug **(ie, at least 1 day before dosing)**. Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

Rationale for Change:

The timing of transfusions was revised to the day before study drug administration.

The following sections also contain this change:

- Section 6.9 Guidance for Clinical Assessment and Management of Hemodynamic Compromise.
- Section 6.10.4 Guidance for Clinical Assessment and Management of Anemia.

Change 13: Updated clinical laboratory evaluations.

The primary changes occurs in Section 7.4.15 Clinical Laboratory Evaluations:

Description of Change:	A footnote was added to the Serum Chemistry parameters list to indicate that assessment of gamma glutamyl transferase is no longer required after completion of Cycle 12. Footnotes were added to the Urinalysis With Microscopic Analysis parameters to indicate that assessment of ketones, bilirubin, urobilinogen, and glucose are no longer required after completion of Cycle 12. A footnote was added to the Urine Safety Assessment to indicate that all assessments are no longer required after completion of Cycle 12.

Rationale for Change:

Assessment of gamma glutamyl transferase, ketones, bilirubin, urobilinogen, glucose, and urine safety assessments are no longer considered necessary for patients continuing beyond 12 cycles of treatment.

Change 14: Remove statins, known breast cancer resistance protein substrates, moderate and strong inhibitors of cytochrome P450 3A4, and inhibitors of P-glycoprotein from the list of excluded concomitant medications.

The primary change occurs in Section 6.6 Excluded Concomitant Medications and Procedures:

Description of Change	Statins, known BCRP substrates, moderate and strong inhibitors of CYP3A4, and inhibitors of P-gp were removed from the list of excluded concomitant medications in Table 6-4.

Rationale for Change:

Statins, known BCRP substrates, moderate and strong inhibitors of CYP3A4, and inhibitors of P-gp are no longer prohibited for MLN4924 therapy. In vitro hepatocyte studies demonstrated that the risk of an MLN4924-statin interaction is low. A review of the available PK information showed that individual daily systemic exposures of MLN4924 were generally similar between statin users (atorvastatin and simvastatin) and non-statin users. As a result of these investigations, the MLN4924 clinical/safety team and the MLN4924 independent data monitoring committee endorsed the removal of the protocol restriction on statin use.

Preliminary data from 11 patients who completed protocol-specified dosing and PK evaluations to assess the effect of itraconazole, a strong CYP3A inhibitor and P-gp inhibitor, on MLN4924 PK indicated that systemic exposures of MLN4924 following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole. These data support removing strong CYP3A inhibitors and P-gp inhibitors from the list of prohibited concomitant medications in ongoing and planned MLN4924 clinical studies. The rationale for removing substrates of BCRP from excluded concomitant medications is based on an assessment of the drug-drug interaction potential of MLN4924. When viewed in the context of the MLN4924 mean C_{max} observed at the established MTD of 20 mg/m^2 for the combination of MLN4924 plus azacitidine in Study C15009, MLN4924 is unlikely to inhibit the drug efflux transporter and hence affect the PK of other drugs that are known BCRP substrates.

The following sections also contain this change:

- Section 5.2 Exclusion Criteria.
- Section 6.5, Dose-Modification Guidelines (Dose Delays, Dose Reductions, and Dose Interruptions); Table 6-3, Dose Modification Guidelines for Specific Toxicities.
- Section 15.7 Excluded CYP3A Inducers.

Change 15: Replace references to the Safety Management Attachment with references to the Development Core Safety Information.

The primary change occurs in Section 1.5.1 Risks of MLN4924 Therapy:

Initial wording:	Additional information on risks is provided in the IB and the Safety Management Attachment to the IB.
Amended or new wording:	Additional information on risks is provided in the IB and the ~~Safety Management Attachment~~ **Development Core Safety Information (DCSI)** to the IB**.**

Rationale for Change:

The content of the Safety Management Attachment has been incorporated into the DCSI, which renders the Safety Management Attachment obsolete.

Section 6.10 Management of Clinical Events also contain this change.

Change 16: Update the description of the Safety Management Team to be consistent with current preferred language and to reflect its cross-functional nature.

The primary change occurs in Section 9.1 Millennium Safety Assessments:

Initial wording:	Safety data will be reviewed and assessed periodically by a internal safety working group throughout the conduct of the study. These reviews will include a safety physician and clinical physician from the study team, as well as other representation from the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, Regulatory Affairs, Drug Safety Evaluation/Toxicology, and Clinical Operations departments at Millennium. Escalation of safety issues to a senior management cross-functional safety committee will be performed on an ad hoc basis.
Amended or new wording:	Safety data will be reviewed and assessed periodically by ~~an internal safety working group~~ **a Global Pharmacovigilance team and a cross-functional Safety Management Team** throughout the conduct of the study. These **cross-functional** reviews will include a ~~safety physician and clinical physician~~ **Global Safety Lead** from the study team, as well as other representation from **other departments at Millennium such as** ~~the~~ Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, ~~Regulatory Affairs, Drug Safety Evaluation/Toxicology,~~ and Clinical Operations ~~departments at Millennium. Escalation of safety issues to a senior management cross-functional safety committee will be performed on an ad hoc basis~~.

Rationale for Change:

This language was updated to be consistent with preferred terminology across the program and to reflect the cross-functional nature of the teams reviewing safety data.

Change 17: Update contact information for product complaints.

The primary change occurs in Section 11.11 Product Complaints:

Initial wording:

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

Amended or new wording:

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately ~~contact MedComm Solutions (see below) and report the event~~ **report this via the phone numbers or email address provided below**. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

~~**For Product Complaints,**~~
~~call MedComm Solutions at~~
~~877-674-3784 (877 MPI DRUG)~~
~~(US and International)~~

Call Center	Phone Number	Email	Fax
Dohmen Life Science Services (DLSS)	**1-844-662-8532** **Non-toll-free number: 1-510-740-1273**	**GlobalOncologyMedinfo@takeda.com**	**1-800-881-6092**

Rationale for Change:

This contact information was updated to reflect an administrative change.

Change 18: Update contact information for serious adverse event reporting.

The primary change occurs in Section 10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Initial wording:

SAE Reporting Contact Information - North and South America

CCI

Amended or new wording:

SAE Reporting Contact Information~~ - North and South America~~

CCI

Rationale for Change:

This contact information was updated to reflect an administrative change.

Change 19: Update the risks of MLN4924 therapy to be consistent with the current version of the Investigator's Brochure (IB).

The primary changes occur in 1.5.1 Risks of MLN4924 Therapy:

Initial wording:

Safety information gained from clinical studies of MLN4924 and from toxicology studies in rats and dogs has been used to guide the safety evaluation of MLN4924. Additional information on risks is provided in the IB and the Safety Management Attachment to the IB.

Based on preliminary findings from the ongoing clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, the risks of MLN4924 treatment are presented below. It is of note that the identified risks are based on clinical experience with many doses and schedules no longer being

studied.

Identified Risks

- Neutropenia
- Increased heart rate
- Diarrhea
- Nausea
- Vomiting
- Pyrexia
- Liver function test (LFT) abnormal
- Musculoskeletal pain
- Renal failure (see additional information described in detail below)

Potential Risks

- Multi-organ failure that could result in death.
- Gastrointestinal (GI) toxicity including or resulting in dehydration, electrolyte imbalance, and/or GI bleeding.
- Endocardial and cardiac vascular changes that could result in tachycardia, cardiac arrhythmias, decreased or increased systolic blood pressure, and increased diastolic blood pressure.
- Acute phase response.
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia.
- Hypophosphatemia.
- Effects on the testes and ovaries that represent a reproductive hazard, including sterility.
- Increased developmental risk to the fetus or embryo.
- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Local tissue injury when administered SC.
- Prolongation of the activated partial thromboplastin time (aPTT).
- Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high). This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.

A comprehensive review of the clinical trial safety data has shown that toxicities on Cycle 1 Day 1, including some events of renal failure with a fatal outcome, have been observed in all MLN4924 studies. Based on the observation that initial doses of IV MLN4924 equal to or above 110 mg/m^2 are associated with more severe AEs, including renal failure, the sponsor has determined that new

patients will receive MLN4924 at doses equal to or below 100 mg/m^2. The current understanding of the renal toxicity observed with MLN4924 suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response.

Multi-organ failure (including hepatic, renal, and/or cardiac) has been reported as an adverse drug reaction with a fatal outcome in patients who have received MLN4924 on Cycle 1 Day 1 at doses equal to or greater than 110 mg/m^2. In addition, a treatment-related death from multi-organ failure was reported in Study C15001 in a patient with breast cancer who received 5 consecutive daily doses of MLN4924 (Cycle 1 Day 5) at 61 mg/m^2. To mitigate the risk of multi-organ failure, studies with MLN4924 doses equal to or greater than 110 mg/m^2 are no longer being initiated in newly enrolled patients. Additionally, a consecutive daily dosing schedule (Days 1-5) is no longer being used. In this study, patients will be administered MLN4924 on a Day 1, 3, and 5 schedule at doses up to 50 mg/m^2 or on a Day 1, 8, and 15 schedule at doses up to 100 mg/m^2. Patients will be monitored closely for events of multi-organ failure after MLN4924 dosing.

Hepatotoxicity has been noted following administration of MLN4924 in patients with advanced malignancy, including elevations of liver transaminases, alkaline phosphatase (ALP), and bilirubin. Liver enzymes and liver function are frequently monitored during clinical studies of MLN4924. Agents such as acetaminophen and acetaminophen-containing products should not be administered to patients 24 hours before, the day of, and 24 hours after dosing with MLN4924 (see Section 6.6).

Patients must be carefully evaluated at screening and before each MLN4924 dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Guidance on rehydration is provided in Section 6.9.

These potential toxicities will be managed by careful, frequent monitoring and intervention, as needed, with supportive care. It is possible that MLN4924 will have toxicities that were not observed in, or predicted from, the studies completed in rats and dogs or have not yet been identified in patients.

Patients will be monitored closely for these anticipated and potential toxicities and for unanticipated toxicities when they are receiving this agent and for at least 30 days after their last dose. Monitoring will include the following: laboratory assessments, physical examinations, SAE and AE reporting, and safety review before each dose escalation (see Section 9.1). In addition, an independent data monitoring committee (IDMC, see Section 9.2) is in place that will monitor the safety data from studies within the MLN4924 program. Although therapeutic efficacy is a desired outcome of treatment with the study drugs, it is unknown whether patients will benefit from this study. In this dose escalation study, the dose will be escalated by cohort.

To limit the risks to patients, the first patient enrolled at each dose level of

MLN4924 with SoC, as applicable, will be observed for 7 days before the remaining 2 patients of the cohort are treated. These 3 patients will be observed through completion of the first cycle, before additional patients are treated at the next dose level. The requirement for this 1-week wait period may be removed in subsequent cohorts if it is judged by the sponsor that combination therapy administered in a given arm may be administered without a major safety concern.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International Conference on Harmonisation [ICH] guidelines).

Amended or new wording:

Safety information gained from **single-agent** clinical studies of MLN4924 and from toxicology studies in rats and dogs has been used to guide the safety evaluation of MLN4924. Additional information on risks is provided in the IB and the **Development Core Safety Information (DCSI)** ~~Safety Management Attachment~~ to the IB.

Based on preliminary findings from the ~~ongoing~~ **single-agent** clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, the risks of MLN4924 treatment are presented below. ~~It is of note that the identified risks are based on clinical experience with many doses and schedules no longer being studied.~~

Identified Risks

- ~~Neutropenia~~
- Increased heart rate
- Diarrhea
- Nausea
- Vomiting
- Pyrexia
- Liver function test (LFT) abnormal
- Musculoskeletal pain
- **Myalgia** ~~Renal failure (see additional information described in detail below)~~

Potential Risks

There are potential risks in the MLN4924 program that require further monitoring. While the potential toxicities listed below may be severe or life-threatening, it is anticipated that they can be managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities for at least 30 days after their last dose of MLN4924.

Potential Risks From Phase 1 Studies (at High Doses)

There are events that have been reported in phase 1 studies at doses and schedules substantially higher (≥110 mg/m^2) than those being used in current clinical studies of MLN4924. These events are considered potential risks for the doses and schedules proposed in this study.

- Multi-organ failure that could result in death.
- **Renal failure.**
  - **The events of multi-organ failure (hepatic, renal, and cardiac) with a fatal outcome, and renal failure alone, have been reported at doses of MLN4924 ranging from 110 to 278 mg/m^2. Refer to the current IB for additional information about multi-organ failure and dosing.**
- **Cardiac arrhythmias.**
  - **All events were supraventricular arrhythmias; all except 1 were unrelated. The case of atrial fibrillation, assessed by the investigator as related, occurred in a patient with a risk factor for cardiovascular disease (uncontrolled hypertension).**
- Gastrointestinal (GI) toxicity including or resulting in dehydration~~,~~ **and** electrolyte imbalance~~, and/or GI bleeding~~.
- ~~Endocardial and cardiac vascular changes that could result in tachycardia, cardiac arrhythmias, decreased or increased systolic blood pressure, and increased diastolic blood pressure.~~
- Acute phase response.
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia.
- Hypophosphatemia.

Potential Risks Confounded by Underlying Disease or Malignancy

Events have been reported from clinical studies that are confounded by the patient's underlying medical condition, including malignancy. These events are noted in the absence of randomized, controlled data:

- **Fatigue**
- **Chills**
- **Decreased appetite**
- **Neutropenia**
- **Febrile neutropenia**
- **GI bleeding**
  - **All events were assessed by the investigator as unrelated; the majority occurred in the setting of thrombocytopenia.**

Potential Risks Primarily Based on Findings From Animal Studies

Potential risks that are derived from findings in animal studies in rats and dogs include the following:

- **Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure (BP), and increased diastolic BP.**
- **Enteropathy (including dehydration and electrolyte loss) with secondary sepsis.**
- Effects on the testes and ovaries that represent a reproductive hazard, including sterility.
- Increased developmental risk to the fetus or embryo.
- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Local tissue injury when administered SC.
- Prolongation of the activated partial thromboplastin time (aPTT).
- Decreased trabecular bone (graded minimal to moderate) was noted in the femur and in the sternum in rats at all dose groups (low, medium, high)**, but not in dogs**. This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.

~~A comprehensive review of the clinical trial safety data has shown that toxicities on Cycle 1 Day 1, including some events of renal failure with a fatal outcome, have been observed in all MLN4924 studies. Based on the observation that initial doses of IV MLN4924 equal to or above 110 mg/m^2 are associated with more severe AEs, including renal failure, the sponsor has determined that new patients will receive MLN4924 at doses equal to or below 100 mg/m^2. The current understanding of the renal toxicity observed with MLN4924 suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response.~~

~~Multi-organ failure (including hepatic, renal, and/or cardiac) has been reported as an adverse drug reaction with a fatal outcome in patients who have received MLN4924 on Cycle 1 Day 1 at doses equal to or greater than 110 mg/m^2. In addition, a treatment-related death from multi-organ failure was reported in Study C15001 in a patient with breast cancer who received 5 consecutive daily doses of MLN4924 (Cycle 1 Day 5) at 61 mg/m^2. To mitigate the risk of multi-organ failure, studies with MLN4924 doses equal to or greater than 110 mg/m^2 are no longer being initiated in newly enrolled patients. Additionally, a consecutive daily dosing schedule (Days 1-5) is no longer being used. In this study, patients will be administered MLN4924 on a Day 1, 3, and 5 schedule at doses up to 50 mg/m^2 or on a Day 1, 8, and 15 schedule at doses up to 100 mg/m^2. Patients will be monitored closely for events of multi-organ failure after MLN4924 dosing.~~

It is possible that MLN4924 will have toxicities, which may be severe or fatal, that were not observed in or predicted from the studies completed in rats and dogs or have not yet been identified in patients.

Hepatotoxicity has been noted following administration of MLN4924 in patients with advanced malignancy, including elevations of liver transaminases, alkaline

phosphatase (ALP), and bilirubin. Liver enzymes and liver function are frequently monitored during clinical studies of MLN4924. Agents such as acetaminophen and acetaminophen-containing products should not be administered to patients 24 hours before, the day of, and 24 hours after dosing with MLN4924 (see Section 6.6).

Patients must be carefully evaluated at screening and before each MLN4924 dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Guidance on rehydration is provided in Section 6.9.

These potential toxicities will be managed by careful, frequent monitoring and intervention, as needed, with supportive care. It is possible that MLN4924 will have toxicities that were not observed in, or predicted from, the studies completed in rats and dogs or have not yet been identified in patients.

Patients will be monitored closely for these anticipated and potential toxicities and for unanticipated toxicities when they are receiving this agent and for at least 30 days after their last dose. Monitoring will include the following: laboratory assessments, physical examinations, SAE and AE reporting, and safety review before each dose escalation (see Section 9.1). ~~In addition, an independent data monitoring committee (IDMC, see Section 9.2) is in place that will monitor the safety data from studies within the MLN4924 program.~~ Although therapeutic efficacy is a desired outcome of treatment with the study drugs, it is unknown whether patients will benefit from this study. In this dose escalation study, the dose will be escalated by cohort.

To limit the risks to patients, the first patient enrolled at each dose level of MLN4924 with SoC, as applicable, will be observed for 7 days before the remaining 2 patients of the cohort are treated. These 3 patients will be observed through completion of the first cycle, before additional patients are treated at the next dose level. The requirement for this 1-week wait period may be removed in subsequent cohorts if it is judged by the sponsor that combination therapy administered in a given arm may be administered without a major safety concern.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International ~~Conference on~~ **Council for** Harmonisation [ICH] guidelines).

Rationale for Change:

The language and content of this section were updated based on the current version of the IB.

Change 20: Clarify the duration of gemcitabine administration per the prescribing information guidelines, as stated in Administrative Letter 1.

The primary change occurs in 6.1.5 Gemcitabine Administration:

Initial wording:	Gemcitabine will be administered as a 1-hour IV infusion at a dose of 1000 mg/m^2 on Day 1 combined with escalating IV doses of MLN4924 on Days 1, 8, and 15. Refer to the most recent prescribing information for further details regarding gemcitabine administration.
Amended or new wording:	Gemcitabine will be administered as a ~~1-hour~~ **30- to 60-minute** IV infusion ~~at a dose of 1000 mg/m^2 on Day 1 combined with escalating IV doses of~~ **before** MLN4924 on Days 1, 8, and 15 **or per current prescribing guidelines**. Refer to the most recent prescribing information for further details regarding gemcitabine administration.

Rationale for Change:

The prescribing information for gemcitabine dictates that gemcitabine can be given over various durations, therefore the text has been modified for clarity and to reflect study conduct.

The following sections also contain this change:

- Protocol Summary.
- Section 4.1 Overview of Study Design.

Change 21: Clarify the collection time points for the urine safety assessment at screening and Cycle 1 Day 1 (predose), as stated in Administrative Letter 2.

The primary change occurs in the Schedules of Events: Cycle 1: Arm 1 and Arm 2:

Description of change:	Footnote "e" was removed from the Urine Safety Assessment in the Cycle 1 Day l assessment tables for all arms. The following language in footnote "l" has been removed: ~~(within 3 days of Cycle 1 Day 1)~~. Footnote "l" now states: "Urine samples for safety assessments will be collected at screening; before any study drug dosing on Days 1, 3, and 5; and on Day 2. These samples will be analyzed at a central laboratory."

Rationale for Change:

The collection time points for urine safety assessment at screening and Cycle 1 Day 1 are unclear because of footnotes “e” and “l”, which provide contradicting information. The intent of the protocol is to obtain 2 baseline urine safety assessments before dosing on Cycle 1 Day l.

The Schedules of Events: Cycle 1: Arm 3 also contains this change.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	19-Oct-2017 17:38 UTC
	Clinical Approval	19-Oct-2017 18:30 UTC
	Biostatistics Approval	19-Oct-2017 19:00 UTC
	Clinical Pharmacology Approval	19-Oct-2017 20:52 UTC